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Microwave-Assisted Rearrangement of Costunolide Catalyzed by Palladium(II)

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The structure of costunolide was modified before conducting the Cope rearrangement under thermal conditions. This modification was undertaken to block the highly reactive Michael acceptor α-methylene-γ-lactone, thus preventing side reactions at high temperatures. In this work, the reaction was performed under heating or microwave irradiation using costunolide, not its modified version. Rates of Cope reactions catalyzed by palladium(II) assisted by microwave were substantially enhanced. The rearrangements of costunolide to elemanolide, eudesmanolides, and germacranolide were catalyzed by palladium acetate, bis(benzonitrile)palladium dichloride, and a mixture of both organometallics. Rates of microwave promoted rearrangements of costunolide were six times faster than the reactions assisted by heating. The best success rate for elemanolide (**7**) was obtained using a mixture of $Pd(OAc)_2$ and $(NCPh)_2PdCl_2$. In this case, compound **7** was obtained in a yield of 34%, while the other sesquiterpene lactones were formed only in trace amounts. The reaction products were isolated using semi-preparative high performance liquid chromatography and further purified through sequential analytical high performance liquid chromatography. Bioactivity profiles that used etiolated wheat coleoptiles were conducted for compounds **6**, **7**, and **9**. The tested compounds presented very high phytotoxicity, with inhibition up to 97%.

Keywords: Cope reaction, sesquiterpene lactone, wheat coleoptile, rearrangement reaction

Introduction

The traditional heating techniques used in organic preparations, such as oil and sand baths, are relatively slow, and localized overheating can result in undesired by-products and substrate decomposition. In contrast, microwaves directly supply energy to the reactants and solvent, rather than to the reaction vessel itself. As a result, the temperature increase induced by microwave heating is uniform throughout the sample, resulting in fewer by-products. Microwave heating is faster than conventional heat sources, and superheating can be rapidly achieved in pressurized reaction vessels.[1-3]

Sesquiterpene lactones are secondary metabolites of plant origin whose chemical structure is based on a 15-carbon skeleton (thus the prefix sesqui) resulting from biosynthesis involving three isoprene units with a cyclic structure containing an α,β-unsaturated-γ-lactone moiety.[4] According to their carbon skeletons, sesquiterpene lactones are classified into germacranolides (**1**), eudesmanolides (**2**), xanthanolides (**3**), guaianolides (**4**), and pseudoguaianolides (**5**) (Figure 1).[5,6]

Sesquiterpene lactones display a broad spectrum of biological activities, including antiviral, trypanocide,[7]

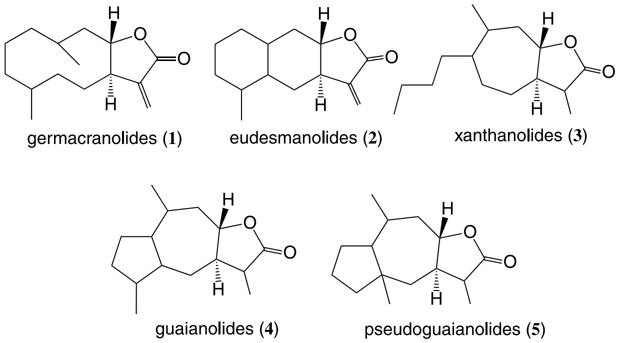

Figure 1. Basic skeleton of sesquiterpene lactones subclass: eudesmanolide, guaianolide, pseudoguaianolide, germacranolide, and xanthanolide.

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antiparasitic,[6] antiprotozoal,[8] anticancer,[6,9,10] anti-inflammatory,[6,10,11] antimalarial,[12] antimicrobial,[13] antioxidant,[10,14] neuroprotective,[15] hepatoprotective,[10] immunoregulatory,[11] immunosuppresant,[16] and other properties.

The literature describes the use of conventional heating under reflux for performing Cope rearrangement of germacranolides, but microwave-assisted reactions have not been reported.[17,18]

Enhancement of the Cope reaction rate was achieved with the use of palladium dichloride[19] and bis(benzonitrile) palladium(II) catalysis. This study aims to evaluate the effects of both heat and microwave irradiation in the Cope rearrangement of costunolide, catalyzed by $Pd(OAc)_2$, $[(PhCN)_2PdCl_2]$, and a mixture of both organometallic catalysts.

The germacrane sesquiterpenes are characterized by the *trans*,*trans*-cyclodeca-1(10),4(5)-diene ring system. Due to their sensitivity to acid and high temperatures, isolating and purifying them from natural sources is challenging.[20,21] With modern agricultural techniques heavily reliant on agrochemicals,[22] we continue our systematic study of sesquiterpene lactones as natural herbicide models. In this context, we present the results of bioassays conducted on etiolated wheat coleoptiles[23,24] using costunolide (**6**), elemanolide (**7**), ß-cyclocostunolide (**8**), eudesmanolide (**9**), γ-cyclocostunolide (**10**), and melampolide (**11**) (Figure 2).

One of the advantages of the wheat coleoptile bioassay is its speed (24 h) and high sensitivity to a variety of bioactive substances, such as plant growth regulators, herbicides, antimicrobials, mycotoxins, and various pharmaceuticals.[24]

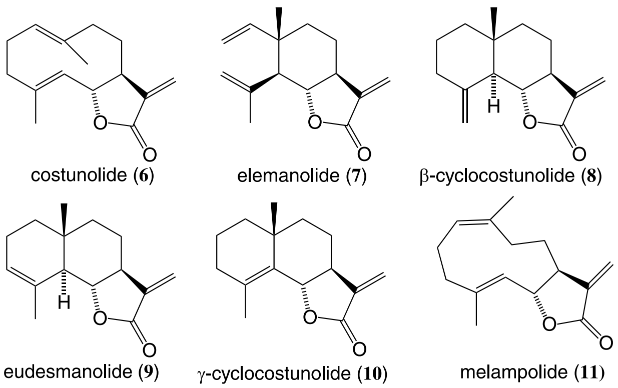


Figure 2. The products **7**-**11** were formed from the rearrangement of costunolide (**6**).

Experimental

All reagents and solvents were purchased from Sigma-Aldrich (Milwaukee, WI, USA).

Synthetic procedures

Costunolide (**6**) was obtained from costus resin oil (*Saussurea lappa*) through column chromatography separation using hexane/ethyl acetate eluent (95:5). Derivatives **7**, **8**, **9**, **10**, and **11** were prepared by microwave-assisted rearrangement of costunolide catalyzed by bis(benzonitrile)palladium(II) chloride $[(PhCN)_2PdCl_2]$ and palladium(II) acetate ($Pd(OAc)_2$). The structures of all compounds were confirmed by comparing their spectroscopic data with the literature.[25-30] Compounds **6**, **7**, **8**, and **9** were separated by high performance liquid chromatography (HPLC, Shimadzu LC, model Workstation CLASS LC-10, Kyoto, Japan) using semipreparative LiChrospher® 100 RP-18 LiChroCART® 250-4 column (5 µm particle size, length × inside diameter 25 cm × 4 mm, Figure 3) and analytic column LC-18 SUPELCOSIL™, (5 µm particle size, length × inside diameter 25 cm × 4.6 mm) and refractive index detector, and characterized by ^1H, ^{13}C, HSQC (heteronuclear single quantum correlation), and HMBC (heteronuclear multiple bond coherence) nuclear magnetic resonance (NMR) spectra. Compounds **10** and **11** were isolated in minimal quantities and identified using ^1H NMR (Varian Inova 400 MHz spectrometer equipped with a 5 mm ^1H-^{13}C dual probe head ASW-PFG, Palo Alto, CA, USA).

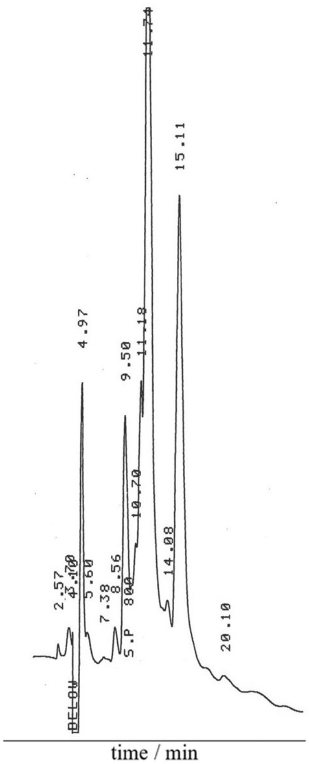


Figure 3. Representative chromatogram of the products from the microwave-assisted costunolide reaction obtained on a semi-preparative column using 20% hexane-acetate eluent. Compounds **6** (15.11 min), **7** (11.74 min), **8** (4.97 min), and **9** (9.50 min).

Rearrangement of costunolide (**6**)

Microwave assisted

Compound (**6**, 10 mg) was dissolved in 1 mL of benzene (or toluene) and added to a transparent glass bottle (16 × 42 mm, 5 mL) containing 1 mg of either $Pd(OAc)_2$ or $[(PhCN)_2PdCl_2]$, or a mixture of $Pd(OAc)_2$ and $[(PhCN)_2PdCl_2]$. The bottle was capped with a screw-on polypropylene cap and the mixture was irradiated at 20 s intervals until reaching a total of 5 or 10 min in a household microwave (Samsung, model MC32J7055CT) operating at 300 W. The reaction was conducted using the rotating plate of the household microwave. At the end, the reaction mixture was filtered through a celite pad in a Pasteur pipette to remove the catalyzer, and the solvent was evaporated by a flow of air. The residue was dissolved in deuterated benzene, transferred to an NMR tube, and the spectra were obtained.

Celite heating bath

Alternatively, the reaction mixture was heated at 80 ºC for 30 min in a celite heating bath. After this period, the mixture was filtered through a pad of celite in a Pasteur pipette and the solvent evaporated by a flow of air. The residue was dissolved in deuterated benzene and ^1H NMR was obtained to calculate the yield of each product in the reaction mixture. The yield was calculated using the integration of the signals in the regions of δ 4.27-3.2 and δ 5.10-6.40 in the ^1H NMR.

Bioassay methodology

The wheat coleoptile straight growth test was used for the bioassay. Wheat seeds (*Triticum aestivum*) were sown on 15 cm diameter Petri dishes fitted with moist filter paper and grown at 25 ºC in the dark for 3 days. Coleoptiles 25 to 35 mm long were selected under a green safelight. A 3 mm section from the tip was cut off and discarded and the next 4 mm was selected for the bioassay. After cutting, the coleoptiles were kept in distilled water for 1 h, then selected at random and placed in vials containing the test solutions. Cutting was done with a Van der Weij coleoptile guillotine.

Fractions were tested at 1000, 500, 250, 125, 75 and 25 µmol L^{-1} in a buffered nutritive aqueous solution (citric acid-sodium hydrogenphosphate buffer, pH 5.6; 2% sucrose). Mother solutions were prepared in dimethyl sulfoxide (DMSO) and diluted to the proper concentration with the buffer to a 0.5% v/v DMSO final maximum concentration. Following dilutions were prepared maintaining the same buffer and DMSO concentrations. Bioassays were performed in 10 mL test tubes as follows: five coleoptiles were placed in each tube containing 2 mL of test solution; three replicates were prepared for each test solution and the experiments were run in duplicate. Test tubes were placed in a roller tube apparatus and rotated at 6 rpm for 24 h at 22 °C in the dark. Increments of coleoptile elongation were measured by digitalization of their photographic images and data were statistically analyzed.

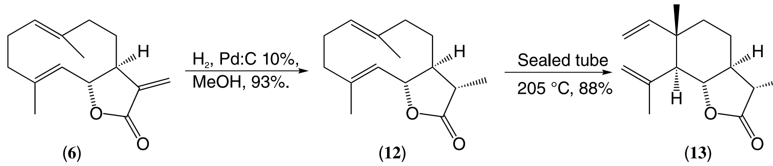
Results and Discussion

Synthesis

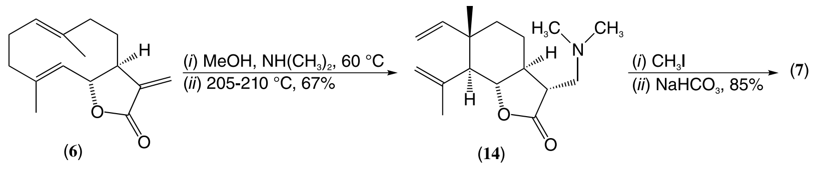
Costunolide was partially hydrogenated before performing Cope rearrangement in a sealed tube at 205 ºC. The hydrogenation of the α-methylene-γ-lactone was done to prevent side reactions on this reactive Michael acceptor at high temperatures. Under thermal Cope rearrangement conditions, an equilibrium mixture of the dihydrocostunolide and the dihydroelemanolide was formed (Scheme 1).[31]

The issue of the α,β-unsaturated methylene γ-lactone unit in the costunolide was addressed by blocking it with dimethylamine, followed by thermal Cope reaction by heating at 205-210 ºC. The elemanolide was subsequently regenerated by base treatment of the quaternary ammonium salt formed (Scheme 2).[32]

Cope rearrangements of costunolide carried out at high temperatures for long periods are described in the literature,[17,18,33] but there are no previous data available about this reaction assisted by microwave. A problem we have observed in this reaction under reflux for long periods was the decomposition of costunolide and an overestimated yield for the elemanolide. Hence, we have evaluated the efficacy of $Pd(OAc)_2$, $[(PhCN)_2PdCl_2]$, and a mixture of both organometallics under microwave and heating conditions for the rearrangement of costunolide. The influence of the solvent was also assessed when employing both heating sources, along with varying heating times using



Scheme 1. Synthesis of dihydroelemanolide (**12**) from costunolide (**6**).



Scheme 2. Synthesis of elemanolide (**7**) from costunolide (**6**).

microwaves, in the formation of the obtained products. The relative proportions of compounds **6-11** were determined by integrating the signals in the regions of δ 4.27-3.2 and δ 5.10-6.40 in the ^{1}H NMR spectra (400 MHz, C_6D_6) of the products obtained in the rearrangement of costunolide under the various evaluated conditions (Figure 4). The results are detailed in Table 1.

The best result obtained by $Pd(OAc)_2$ catalysis was a conversion of only 18% of costunolide. However, the reaction was clean and cyclization products (as compound **9**) were barely detected by ^{1}H NMR.

$[(PhCN)_2PdCl_2]$ catalysis afforded 35% yield of compound **7**, 32% of compounds **8** and **9** plus unreacted starting material (33%). Thus, we have decided to evaluate the outcome of a mixture of $Pd(OAc)_2$ and $[(PhCN)_2PdCl_2]$. Whereas palladium acetate presented low rearrangement conversion but improved selectivity and $[(PhCN)_2PdCl_2]$ afforded higher catalytic power but poor selectivity.

The catalytic mixture afforded the cyclization products **8**, **9**, and **10** in trace amounts and the germacranolide **11** in yields which varied from 5-17%. Compounds **10** and **11** were not observed in the reactions catalyzed by either $Pd(OAc)_2$ or $[(PhCN)_2PdCl_2]$. This fact prompted us to suggest that compounds **10** and **11** are not formed by either $Pd(OAc)_2$ or $[(PhCN)_2PdCl_2]$ alone but by a somehow new entity emerged from the two.

Several chemical transformations were performed on costunolide (**6**) to prepare cyclic derivatives (**7-11**). The mechanism for obtaining elemanolide (**7**) is the Cope type rearrangement, which occurs at high temperatures during conventional heating over several hours.[21,34-36] In this study, the reaction was catalyzed by Pd^{II} complex and carried out in a microwave for 5 or 10 min. Melampolide (**11**) is formed through the isomerization of one double bond. The literature describes the acid-catalyzed cyclization mechanism for the preparation of compounds (**8**) and (**9**).[37] The mechanism for the formation of compounds (**8-10**) catalyzed by Pd^{II} is proposed in Scheme 3.

The catalytic process was conceptualized as a sequential mechanism, wherein the electrophilic nature of Pd^{2+} plays a facilitating role in bond formation. Alkenes react with Pd^{II} to give complexes that are subject to nucleophilic attack. Initially, the palladium catalyst coordinates with one double bond forming a reactive Pd^{II} π complex (intermediate I). This complex then undergoes nucleophilic attack by the double bond α to the lactone to form a new Pd^+ complex

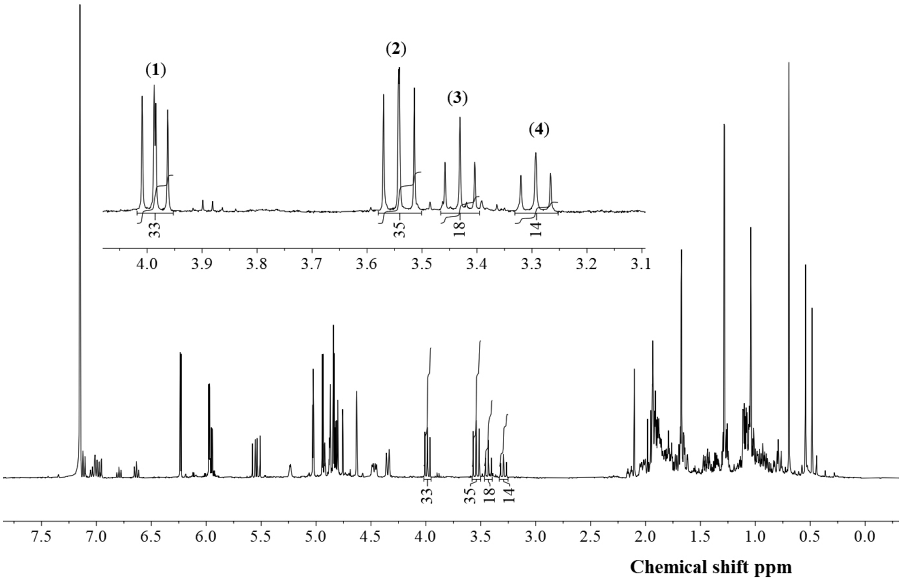


Figure 4. Representative ^{1}H NMR spectrum (400 MHz, C_6D_6) of costunolide (**6**) and the products elemanolide (**7**), ß-cyclocostunolide (**8**), and eudesmanolide (**9**) resulting from the reaction of costunolide using toluene as solvent, $[(PhCN)_2PdCl_2]$ as the catalyst, and microwave irradiation for 5 min. The numbers below each signal represent the integral values used to determine the relative proportions of compounds (**6**), (**7**), (**8**), and (**9**) in the δ 4.27-3.2 region.

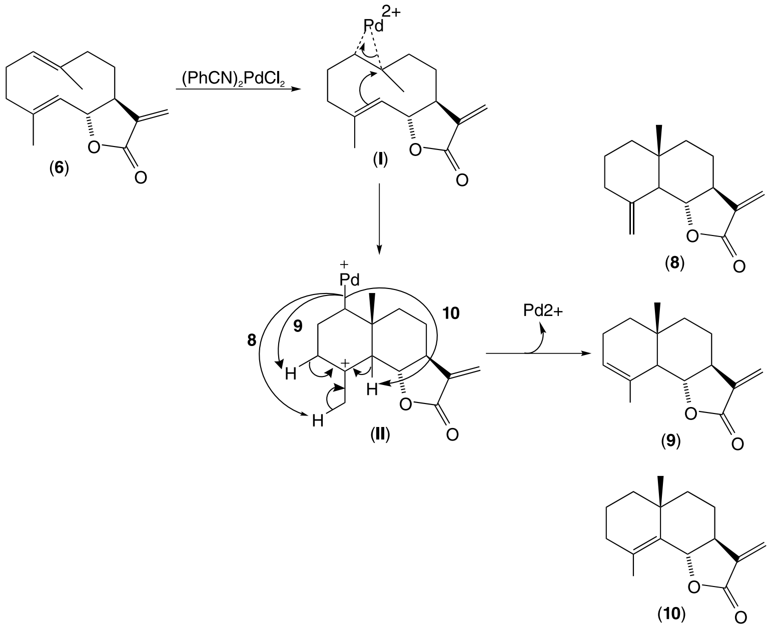
Table 1. Conditions and yields of costunolide rearrangements

entry	Condition[a]	Solvent[b]	Catalyzer[c]	time / min	Relative proportions of each compound[d]					
					6	**7**	**8**	**9**	**10**	**11**
1	80 °C	benzene	–	30	100					
2	80 °C	toluene	–	30	100					
3	80 °C	benzene	$Pd(OAc)_2$	30	100					
4	80 °C	toluene	$Pd(OAc)_2$	30	100					
5	80 °C	benzene	$(NCPh)_2PdCl_2$	30	45	23	15	17		
6	80 °C	toluene	$(NCPh)_2PdCl_2$	30	48	23	15	14		
7	80 °C	benzene	mixture	30	72	22	trace			6
8	80 °C	toluene	mixture	30	59	29	trace			12
9	MW	benzene	$Pd(OAc)_2$	5	100					
10	MW	toluene	$Pd(OAc)_2$	5	100					
11	MW	benzene	$Pd(OAc)_2$	10	95	5		trace		
12	MW	toluene	$Pd(OAc)_2$	10	82	18		trace		
13	MW	benzene	$(NCPh)_2PdCl_2$	5	41	32	15	12		
14	MW	toluene	$(NCPh)_2PdCl_2$	5	40	35	13	12		
15	MW	benzene	$(NCPh)_2PdCl_2$	10	38	35	15	12		
16	MW	toluene	$(NCPh)_2PdCl_2$	10	33	35	18	14		
17	MW	benzene	mixture	5	54	32			trace	14
18	MW	toluene	mixture	5	65	24			trace	10
19	MW	benzene	mixture	10	53	30	trace	trace	trace	17
20	MW	toluene	mixture	10	61	34	trace	trace	trace	5

[a]Reaction heated at 80 °C or microwaved at 300 W; [b]1 mL of solvent; [c]1 mg of one catalyst or a mixture of the catalysts (2 mg); [d]the relative proportions were calculated using the signals in δ 4.27-3.20 in the ^{1}H NMR.

containing the carbon-carbon bond (intermediate II). Finally, reductive elimination occurs, leading to the formation of the naphthalene skeletons (compounds **8**, **9**, and **10**) and regeneration of the palladium catalyst.[19]

The lower-energy compound **10** is formed in trace amounts, possibly due to steric hindrance of the hydrogen located at the junction of the two rings. In contrast, the formation of compounds **8** and **9** is favored over



Scheme 3. The proposed mechanism for obtaining compounds **8-10** from **6** in the Pd^{II}-catalyzed rearrangement reactions performed in a microwave for 10 min.

compound **10**, facilitated by the accessibility of methyl and methylene hydrogens. In the proposed mechanism, the proton was captured by the negative charge generated upon the departure of Pd^{2+}.

The relative proportions of starting material, rearrangement, and cyclization products were not substantially altered by changing the solvent from benzene to toluene. The most pronounced changes were observed in reactions promoted by heat and microwave. While the reactions promoted by heat afforded 23% of the rearranged elemanolide (**7**) after 30 min, the microwaved reactions provided 35% of compound **7** after only 5 min. No substantial progress was observed in the reactions assisted by microwave after 5 min. After 5 min reaction, the formed products exhibit an optimal substitution pattern and relative stability.[38]

Bioassays

Tests using etiolated wheat coleoptiles have been employed to assess the herbicidal potential of secondary metabolites from root exudates and extracts of *Carthamus tinctorius* affected by parasites and weeds,[39] root extracts of *Urochloa humidicola*,[40] extracts from the leaves of *Origanum majorana* L.,[41] furanocoumarins isolated from the aerial parts of *Ducrosia anethifolia*,[42] aminophenoxazinones,[43] C17 sesquiterpenoids (a group of natural products that lack the α,β-methylene butyrolactone system),[44] agave saponins,[45] acyl and alkyl derivatives of juglone and lawonin,[46] and many others.

Six compounds were obtained from the rearrangement of costunolide. Compounds **6**, **7**, and **9** were subjected to a bioassay of etiolated wheat coleoptiles. Six dilutions were used in the assay (1000, 500, 250, 125, 75, and 25 µmol L^{-1}).

The etiolated wheat coleoptile bioassay was employed as a preliminary approach to evaluate the bioactivity of costunolide (**6**) and its derivatives (**7** and **8**) due to its sensitivity towards a broad spectrum of bioactive substances, including herbicides, antimicrobials, mycotoxins, pharmaceuticals, and plant growth regulators.[24,47]

The results obtained from the bioassay are depicted in Figure 5, where negative values indicate inhibition, zero represents the control, and activity levels correlate with the concentration expressed in µmol L^{-1}. The tested compounds exhibited significant activity in the coleoptile bioassay, with inhibition reaching up to 97%. Compound **7** displayed the highest inhibitions at 1000 and 500 µmol L^{-1} (97 and 95%, respectively). Compound **6** demonstrated substantial activity even at 125 µmol L^{-1}, showing inhibition exceeding 90%. Compound **9** exhibited comparatively lower activity but still displayed an inhibition of 87% at 250 µmol L^{-1}.

Conclusions

Catalysis performed by palladium acetate exhibited a low conversion rate of costunolide but high selectivity. Palladium acetate catalysis under heating did not result in the conversion of costunolide. However, under microwave irradiation for 10 min. using toluene as the solvent the elemanolide (**7**) was formed in 18% yield.

The catalyst bis(benzonitrile)palladium(II) chloride exhibited better conversion rate of costunolide but lower selectivity compared to palladium acetate. Using $(NCPh)_2PdCl_2$, the conversion rate reached 60% in toluene, while $Pd(OAc)_2$ catalysis presented a maximum of 18%

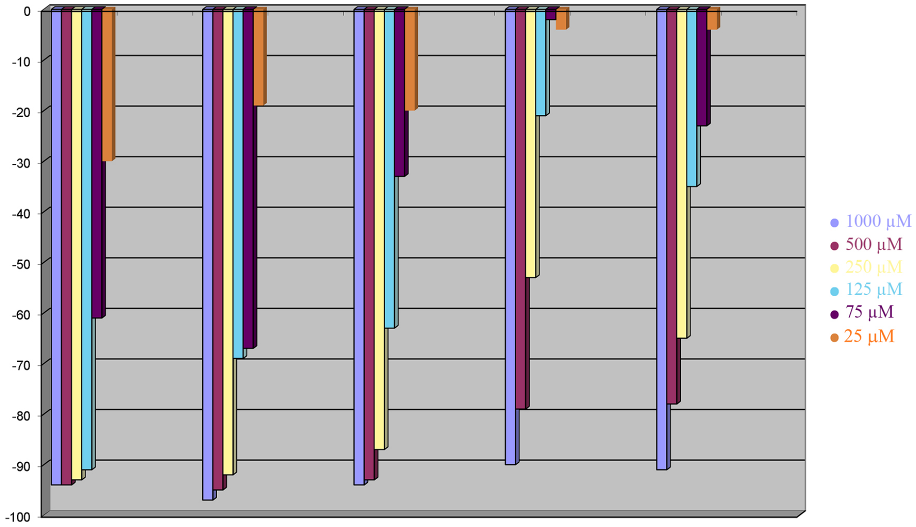


Figure 5. Effects of compounds **6**, **7**, and **9** on the elongation of etiolated wheat coleoptiles. The values are expressed as a percentage relative to the control and were found to be not significantly different ($P > 0.05$) according to the Mann-Whitney test.

conversion of costunolide in the same solvent. Catalysis with $(NCPh)_2PdCl_2$ allowed us to obtain compounds **8** and **9** using either benzene or toluene as the solvent. The choice of solvent or time of irradiation using $(NCPh)_2PdCl_2$ as the catalyst did not significantly influence the yields of compounds **8** and **9**. However, under heating, compounds **7**, **8**, and **9** were formed with yields of 23, 25, and 14%, respectively, while under microwave irradiation, the yields for the same compounds were 35, 13, and 12%.

The compounds that were tested showed noteworthy activity in the coleoptile bioassay, resulting in inhibition levels of up to 97%. Among them, compound **7** exhibited the most pronounced inhibitory effects, with percentages of 97 and 95% observed at concentrations of 1000 and 500 µmol L^{-1}, respectively. Compound **6** demonstrated substantial activity even at a lower concentration of 125 µmol L^{-1}, exhibiting an inhibition rate exceeding 90%. On the other hand, compound **9** displayed relatively lower activity but still managed to achieve an inhibition of 87% at a concentration of 250 µmol L^{-1}.

Therefore, **6**, **7**, and **9** proved to be suitable compounds for further investigation in the development of novel herbicides and plant growth regulators.

Supplementary Information

Supplementary information is available free of charge at http://jbcs.sbq.org.br as PDF file.

Acknowledgments

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