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Palladium II Promoted Rearrangement of Germacranolides. Synthesis of (+)-Stoebenolide and (+)-Dehydromelitensin.

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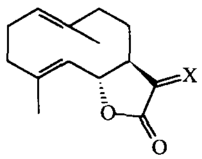
Abstract. Catalytic amounts of bis(benzonitrile)palladium (II) chloride enhanced reaction rates of germacranolides Cope rearrangement to elemanolides. On the other hand, equimolecular amounts of the palladium complex transformed germacranolides into eudesmanolides. These phenomena provide a versatile procedure for the synthesis of eudesmanolides and elemanolides under relatively mild experimental conditions. Thus, (+)-stoebenolide and (+)-dehydromelitensin were alternatively synthesized starting out from (+)-salonitenolide. © 1998 Elsevier Science Ltd. All rights reserved.

(+)-Vernolepin is a natural elemanolide with potent antitumoural[1] and antimicrobial[2] effects. In our work on the synthesis of (+)-vernolepin and related compounds from homochiral germacranolides,[3] we needed a suitable procedure for the rearrangement of the germacrane to the elemane skeleton. Conventional thermal Cope rearrangement of germacranolides, usually carried out in a sealed tube at temperatures of around 210° C, lead to a germacranolide $\rightleftharpoons$ elemanolide equilibrium,[4] and pyrolyse part of the products, offering poor yields in many cases. Palladium dichloride catalyzed Cope rearrangement of several acyclic dienes gave good results,[5] but there are no previous data available about this reaction with germacradienolides in general. Therefore, we have tested the effect of $[PdCl_2(PhCN)_2]$ in the rearrangements of (+)-costunolide[6] (**1**), and its partially hydrogenated derivative (+)-11βH,13-dihydrocostunolide[7] (**2**), in solution (100 mg substrate / 10 ml solvent) and at temperatures 100° C lower. Results are summarized in Table 1. Formation of products **3-8** was proved by means of their isolation by Si gel column chromatography and spectroscopic characterization.[4,8] Their relative proportions were determined on the basis of the ^{1}H NMR spectra of the mixtures formed in every experiment.



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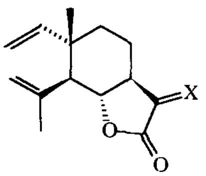
2 X= βH, αCH_3



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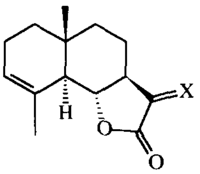

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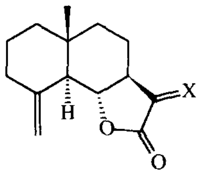
6 X= βH, αCH_3



7 X= CH_2
8 X= βH, αCH_3

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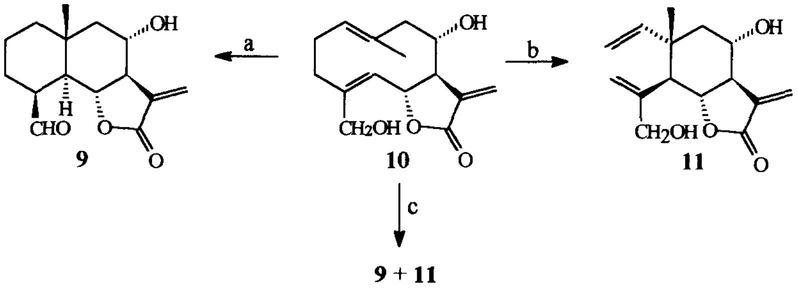
Table 1. Relative Proportions of Unchanged Starting Material and Rearrangement Products Obtained in Catalyzed and Non-catalyzed Rearrangements of **1** and **2**.

Entry	s.m.[1]	exp. cond.[2]	cat. equiv.[3]	Time				
					1	**3**	**5**	**7**
1	**1**	T, reflux	-	24 h	78	22	trace	trace
2	**1**	T, reflux	0.02	4.5 h	77	20	2	1
3	**1**	T, reflux	0.02	24 h	59	35	4	2
4	**1**	B, r.t.	0.1	24 h	32	14	28	26
5	**1**	T, reflux	0.1	4.5 h	28	24	27	21
					2	**4**	**6**	**8**
6	**2**	T, reflux	-	24 h	63	37	trace	trace
7	**2**	T, reflux	0.02	6 h	61	38	1	trace
8	**2**	T, reflux	0.02	24 h	37	50	7	6
9	**2**	T, reflux	1	2 h	-	-	69	24

[1] Starting material ; [2] Experimental conditions: T= toluene, B= benzene, r.t.= room temperature ; [3] Catalyst equivalents.

Data from Table 1 indicate that catalytic amounts of $[PdCl_2(PhCN)_2]$ slightly enhanced the rate of the Cope rearrangements of **1** to **3** and **2** to **4**, at least in the first stages of the reaction (experiments 2 and 7 *versus* 1 and 6, respectively). However, a slow breakdown of the catalyst presumably occurs[5] and, in later stages of experiments 3 and 8, the reaction would evolve by a non-catalyzed thermal process. When the quantity of $[PdCl_2(PhCN)_2]$ was increased, an unexpected rise in the relative proportions of the eudesmanolides **5**-**8** was

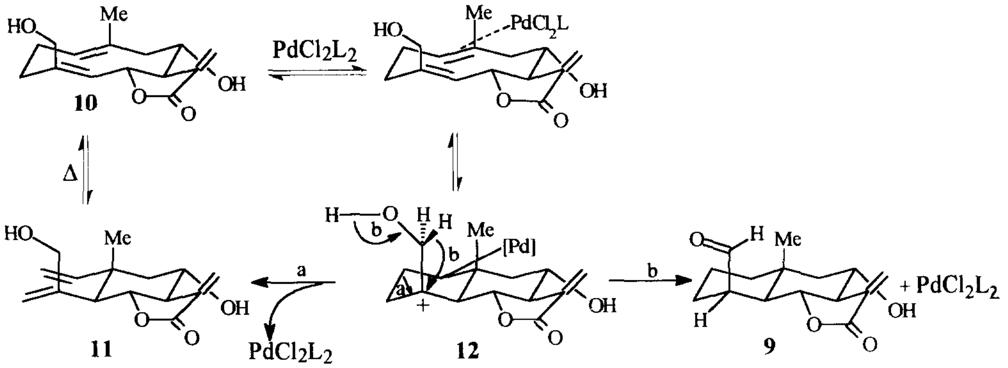


Scheme 1. a) Toluene reflux, an equivalent of $[PdCl_2(PhCN)_2]$, 1h. b) Toluene reflux, 5h. c) Toluene reflux, 0.02 equivalents of $[PdCl_2(PhCN)_2]$, 1h.

observed, and using equimolecular amounts the transformation was almost quantitative. This fact prompted us to attempt enantioespecific synthesis of stoebenolide (**9**), an eudesmanolide found in the plant *Centaurea stoebe*[9] with presumable biological activity (cf. reference 10), starting from (+)-salonitenolide[11] (**10**).

In the non-catalyzed thermal Cope rearrangement of **10**, the germacranolide ⇌ elemanolide equilibrium lay towards the right, and only (+)-dehydromelitensin[12] (**11**) was obtained (Scheme 1). However, when an equimolecular amount of $[PdCl_2(PhCN)_2]$ was employed, the reaction generated (+)-stoebenolide[13] (**9**), and no dehydromelitensin formation was observed. Catalytic amounts of $[PdCl_2(PhCN)_2]$ yielded a mixture of eudesmanolide **9** and elemanolide **11**, in a similar way as occurs with costunolide (**1**). Absolute configuration of (+)-salonitenolide (**10**) is known, because it was chemically correlated with (+)-cnicin,[11] whose absolute stereochemistry was determined by x-ray analysis.[14] Therefore, synthesis of (+)-stoebenolide (**9**) and (+)-dehydromelitensin (**11**), from **10**, confirmed their structures and indicated their absolute configurations (depicted in Scheme 1).

Formation of either elemanolides or eudesmanolides, depending on the relative proportion of $[PdCl_2(PhCN)_2]$ employed, may be explained according to the mechanism depicted in Scheme 2. This scheme illustrates formation of **9** and **11** from **10**, but it might be of general validity. Low amounts of $[PdCl_2(PhCN)_2]$ catalyze formation of **11** (way a) via the carbocationic intermediate **12**, wich is similar to that proposed by Overman and Renaldo[5] to justify the palladium dichloride catalyzed Cope rearrangement of acyclic dienes. However, when higher concentrations of palladium complex are used, its ligands trap the hydroxylic proton, acting as a base, and favour non-reversible formations of **9** (way b).



Scheme 2. Presumable Mechanism for the Palladium Promoted Rearragements of **10**.

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11. (+)-Salonitenolide (**10**) was obtained by selective saponification of the lateral chain of (+)-cnicin isolated from *Centaurea malacitana*. (Barrero, A.F.; Oltra, J.E.; Rodríguez, I.; Barragán, A.; Grávalos, D.G.; Ruiz, P. *Fitoterapia*, **1995**, *66*, 227-230).
12. Oil; $[\alpha]_D$ +56 (c 0.3, $CHCl_3$). Other physical properties match those reported (Cardona, M.L.; García, B.; Pedro, J.R.; Sinisterra, J.F. *Phytochemistry*, **1989**, *28*, 1264-1267).
13. Oil; $[\alpha]_D$ +98 (c 1.2, acetone), ^{13}C NMR ($CDCl_3$, 100MHz) δ 18.0 (t, C-2), 20.4 (q, C-14), 24,2 (t, C-3), 36.1 (s, C-10), 41.0 (t, C-1), 45.8 (d, C-4), 49.7 (d, C-5), 52.6 (t, C-9), 57.0 (d, C-7), 67.4 (d, C-8), 77.0 (d, C-6), 120.3 (t, C-13), 137.6 (s, C-11), 170.0 (s, C-12), 202.9 (d, C-15). Assignment of the ^{13}C NMR spectrum data was performed on the basis of trivial analysis of DEPT and HETCOR experiments. ^1H NMR spectrum match that reported in ref. 9.
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