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Regiochemistry of Palladium(II)-Assisted Oxidative Lactonisation Reactions.

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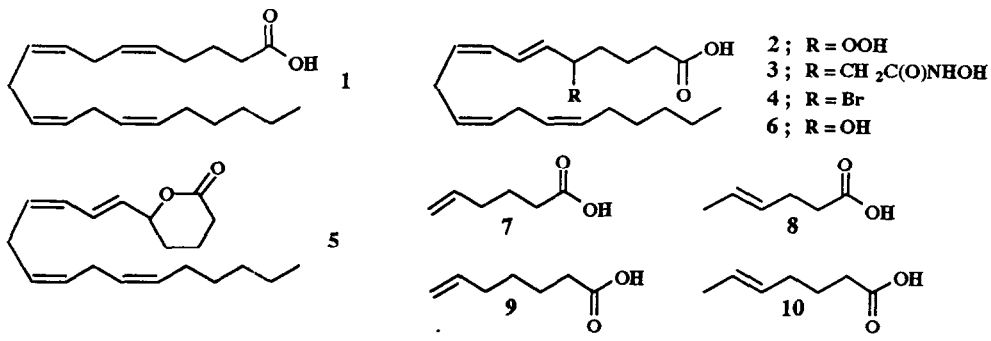
Abstract: The Pd(II)-assisted lactonisation of alkenoic acids has been studied. The selectivity, persisting to formation of 5- and 6-membered unsaturated lactones, can be governed by the change of solvent and/or base.

The study of 5-lipoxygenase (5-LO) inhibitors has become one of the most important fields in anti-inflammatory research. The fact that the enzyme utilises not only arachidonic acid (**1**) but also the initial oxidation product 5-HPETE (**2**) as substrate was exploited already in the early development of 5-LO inhibitors.[1] Since ferric ion is thought to be present in the active site, powerful iron chelators such as hydroxamic acids[2,3] attracted attention initially. For example, Kerdesky *et al.* reported compound **3**, which may be considered as a substrate-like (5-HPETE) analogue, to be a relatively potent inhibitor.[4] Development following this early lead has indeed delivered clinically effective anti-inflammatory hydroxamic acid compounds.[1b]

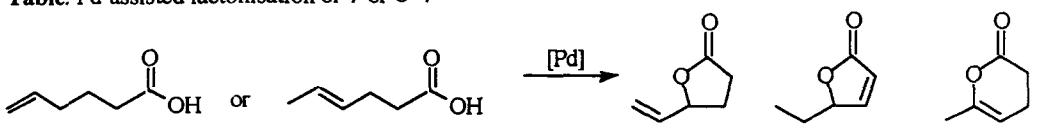
We were interested in assessing further 5-HPETE analogues as starting points for drug development, and needed the bromo derivative **4** as a key intermediate, which in principle should be available from **5**. Although this lactone (**5**) has already been prepared from **1** via either iodolactonisation[5] or selenolactonisation,[6] both these methods seem to suffer drawbacks with regard to selectivity as well as yield.[5b,6] With methods emerging allowing palladium-assisted acetoxylations to be performed catalytically,[7] we wished to see whether oxidative lactonisation would have any potential as a mild route from **1** to **5** and 5-HETE (**6**), but found studies on palladium-assisted lactonisations of alkenoic acids to be rather scarce.[8] The apparent lack of basic insight into the regioselectivity of palladium(II)-assisted lactonisations prompted us to study these reactions using the model substrates **7-10**.

From the Table it is evident that the regioselectivity of lactonisation of **7** is strongly dependent on the choice of both solvent and base. Whereas modest selectivity for the 5-membered product **11** was



observed in DMSO, its double bond isomer (**12**) was also formed in other solvents using Na_2CO_3 as base. Interestingly, the regioselectivity changed to favour the 6-membered lactone **13** upon changing the base to NaOAc in THF. A cleaner reaction could be achieved by using the latter in MeCN. Similar effects favouring **13** were observed when ^{t}BuOK was used as the base in either THF or MeCN. The use of amine bases such as NEt_3 or DBU did not result in improved selectivity. Reaction performed in THF in the absence of a base gave a very complex mixture. It should be noted that the products obtained here are different from those reported by Semmelhack *et al.* who did not observe any 5-membered products from analogous reactions utilising 5-alkenols.[9] The formation of lactones **11** and **12** was somewhat unexpected, since we are aware of only one example of this type of product from similar reactions of 5-alkenols or 5-alkenoic acids. In this instance[8b] it was proposed that prior isomerisation to the 4-alkenoic acid took place. In our case, no isomerised acids could be observed in an experiment (DMSO, $PdCl_2(MeCN)_2$, Na_2CO_3) where the reaction was quenched at low conversion. The δ–lactone **13** could be isolated in 55 % yield and hydrolysed (Et_3N/MeOH) to 5-oxo-methylhexanoate to further support the structure. In DMSO, the lactonisation of **8** was much more selective, and only **11** was observed. This product was isolated in 60 % yield. The absence of isomerised γ–lactone **12** in DMSO is in agreement with previous experience from alkenol annelations.[9, 10] On the other hand, Kasahara *et al.* [8a] isolated **12** as the sole product from the same starting material (**8**), but using Li_2PdCl_4 and Na_2CO_3 in aqueous solution. In our hands, similar conditions resulted in complex mixtures of isomeric lactones, of which **11** usually was the most abundant. We also applied the most useful conditions to the substrates **9** and **10** (equation 1). Both compounds gave **14** (NMR, MS) as the main product in DMSO/Na_2CO_3, whereas the MeCN/NaOAc system delivered two products from **10** in an 8:2 ratio, the main one being **15** (NMR, MS, confirmed by conversion into 5-oxo-methylheptanoate). Under the latter conditions, **9** gave a complex mixture which did not contain **15**. The presence of a higher boiling byproduct has so far prevented the isolation of **14** from the former reaction. It was observed, as in the previous cases, that the reaction in DMSO was very much slower than in MeCN. In DMSO, the addition of Bu_4NCl did not seem to have any profound effect

Table. Pd-assisted lactonisation of **7** or **8** [a].



7 **8** **11** **12** **13**

Acid	Solvent	Base	Reaction time (h)	Products (%) [b]			
				11	**12**	**13**	isomers [c]
7	DMSO	Na_2CO_3	28-46	70		30	
7	MeCN	Na_2CO_3	27-46	15	15	70	
7	DMF	Na_2CO_3	46	25	10	65	
7	Acetone	Na_2CO_3	46	10	60		30
7	Toluene	Na_2CO_3	8	30	20		50 [d]
7	THF	Na_2CO_3	8-28	10	60		30
7	THF [e]	NaOAc	7			75	25
7	MeCN	NaOAc	4-6	10		90 [f]	
7	DMSO	----- [g]	72-96	70		30	
7	THF	^{t}BuOK	6	20		80	
7	MeCN	^{t}BuOK	6	10		90	
8	DMSO	Na_2CO_3	24	100 [h]			
8	THF	Na_2CO_3	5	10	60		30
8	MeCN	Na_2CO_3	3	30	30		30

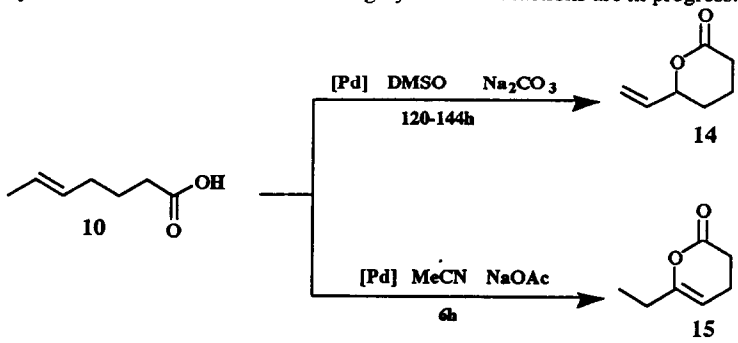
[a] The reactions were performed at room temperature in 4-10 ml of solvent with 0.05-0.1 mmol of **7** or **8**, base (1.1-2.0 equiv.) and $PdCl_2(MeCN)_2$ (1.1-1.5 equiv.) if not stated otherwise. [b] The product compositions given are averages of at least two experiments and were determined by GC assuming equal response factors for all isomers. Reactions were run until the acid was consumed and in cases where internal standard was used the lactones usually accounted for 70-100% of the starting amount of acid. The structures of **11-13** were determined by NMR analyses of isolated material. [c] Isomeric lactones according to GC-MS analyses. [d] Assuming isomeric lactones. [e] [Pd] = $Pd(OAc)_2$. [f] Isolated in 55% yield from 1 mmol of **7**. [g] The sodium salt of **7** was used. [h] Either $PdCl_2(MeCN)_2$ or $Pd(OAc)_2$ was used. Lactone **11** was isolated in 60% yield from 1 mmol of **8**.

on the rate of conversion of **7**.

In analogy with the intermolecular acetoxylations, two pathways can be envisaged for the formation of **11-13**. The intramolecular attack of carboxylate on a η^2-alkene complex should account for the formation of **13** from **7**. Similarly, **11** would be produced from **8**, however a η^3-allyl complex would give the same product. Although the formation of **11** and **12** from **7** could be a result of substrate isomerisation, our unability to detect 4-hexenoic acid in the reaction mixture would seem to support the η^3-allyl pathway. Åkermark and coworkers found some evidence for such a mechanism in the acetoxylation of alkenes.[7a] Similar observations were made by Larock *et al* [8d]. We have found no

evidence for extensive formation of **12** from **11**.

We conclude that the Pd-mediated oxidative lactonisation reactions could be valuable in organic synthesis. Further efforts to obtain highly selective reactions are in progress.



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