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STEREOCONTROLLED LACTONIZATION REACTIONS VIA PALLADIUM-CATALYSIS

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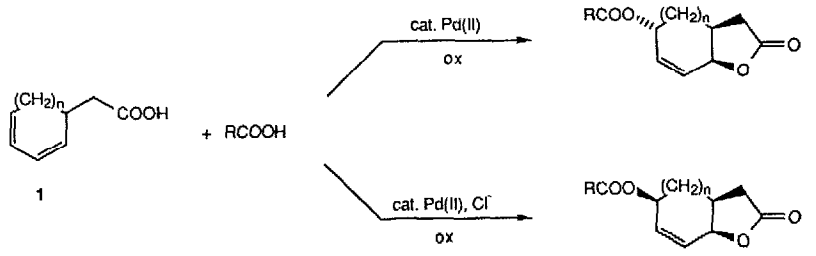
Summary: Dienes **1** were transformed into γ-lactones via a novel stereocontrolled palladium-catalyzed lactonization reaction. The oxylactonization can be directed towards either a *cis*- or *trans*-addition across the diene.

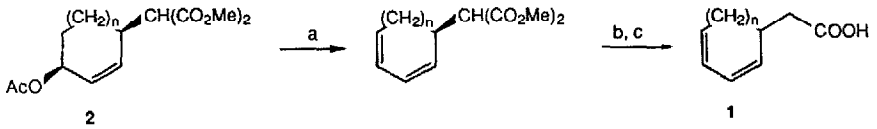
Lactonization reactions of olefins are useful in organic synthesis and are well-described in the literature.[1-6] The iodolactonization[1,2] is probably the most commonly used, but lactonizations via oxymetallation have found increasing use.[3-6] Lactonization reactions of conjugated dienes have also been described and in these cases metallolactonizations give the best selectivity.[4-6]

We have recently reported procedures for stereocontrolled palladium-catalyzed 1,4-oxidations of conjugated dienes.[7-9] It occurred to us that application of these reactions to substrates **1** may lead to interesting lactonization reactions. We now report a stereocontrolled palladium-catalyzed lactonization reaction of cyclic diene substrates **1**, which offers a choice between *trans*- and *cis*-1,4-oxylactonizations (Scheme 1).

Scheme 1



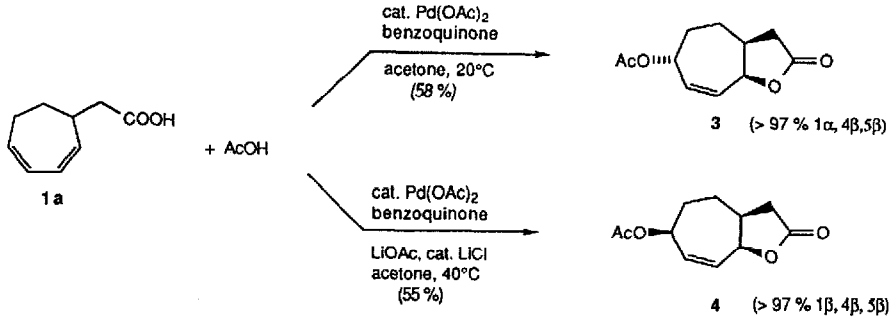
The dienes **1** were prepared from the corresponding compounds **2**, which are readily available in good yields from 1,4-functionalization of the corresponding diene (85-88%, n=1; 72%, n=2).[9,10] Palladium-catalyzed elimination of acetic acid[10,11] and subsequent decarboxylation-hydrolysis afforded **1** (eq. 1). Attempts to cyclize



(eq. 1)

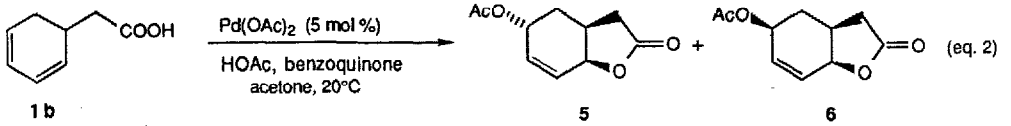
a. $Pd(dba)_2$ (5 mol %), biphos, Bu_3N, toluene 110°C (74-84 %). b. NaCN, wet DMSO, 70°C (81-82 %)
c. KOH, $MeOH/H_2O$, 30°C (95-99 %)

dienes **1** in acetic acid under the conditions employed for palladium catalyzed 1,4-diacetoxylation,[7] gave poor isolated yields of the products partly because of work-up problems.[12] However, use of the recently improved procedure for palladium-catalyzed 1,4-functionalization, developed in our laboratory,[13] resulted in a considerable increase of the yields. Thus, palladium-catalyzed reaction of **1a** in acetone in the presence of



acetic acid using benzoquinone as the oxidant afforded **3** in 58% isolated yield. Analysis of the crude product mixture by ^{1}H NMR showed that more than 97% of one isomer (*1α,4β,5β*) had been formed. When the reaction of **1** was performed in the presence of catalytic amounts of lithium chloride and in addition lithium acetate, but otherwise under the same reaction condition, the other stereoisomer **4** was formed in high selectivity (*> 97% 1β,4β,5β*). The ^{1}H NMR coupling constants were consistent with the structures assigned, and the assignment was confirmed by NOE-experiments.[14]

Reaction of the corresponding 6-membered ring **1b** under the chloride free reaction conditions resulted in the formation of the *1α,4β,5β*-lactone **5** in high stereoselectivity and good yield. For the six-membered ring it was more difficult to direct the stereoselectivity towards a clean 1,4-*cis*-addition. The usual reaction conditions

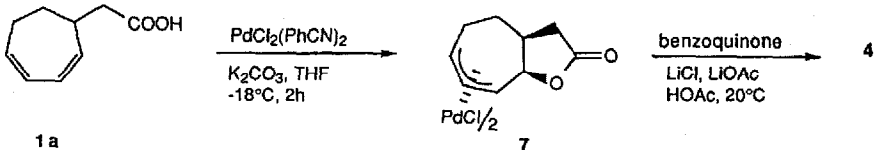


LiOAc (equiv[a].)	LiCl (equiv[a].)			Yield 5 + 6
0	0	99	: 1	77 %
11	0.45	55	: 45	76 %
11	0.68	42	: 58	50 %
2	0.15	42	: 58	50 %
2	0.50	24	: 76	57 %

[a] towards diene

with 0.1-0.3 equivalents of LiCl and 2M LiOAc (11 equivalents) still afforded < 50% of the β,β,β-isomer **6**. Unexpectedly,[15] a better selectivity for 1,4-*cis*-addition was obtained at a lower acetate concentration. Thus the use of 2 equivalents of LiOAc (~ *0.4 M*) and *0.5 equivalents of LiCl* afforded a 24:76 ratio between **5** and **6**.

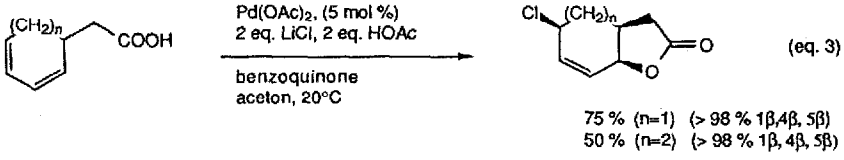
In order to gain some insight into the mechanism, we prepared and isolated the presumed catalytic intermediate as the chloride dimer **7**. Reaction of **1a** with $PdCl_2(PhCN)_2$ in acetone afforded **7** as a yellow crystalline compound in 71% yield. The presence of a γ-lactone was evident from the IR spectrum (1787 cm^{-1})



and the *cis*-lactone configuration follows from the ^{1}H NMR spectrum.[16] The *trans* relationship between palladium and oxygen was confirmed by reaction of **7** with acetate under conditions for external *trans*-attack,[17] which afforded **4**.

It is now well documented[7,17] that the role of the lithium chloride in these stereocontrolled catalytic reactions is to block the coordination of the carboxylate, and hence favor an external attack by acetate. In the absence of chloride ions, the ligand on palladium will be acetate and the product may be formed through a *cis*-migration, most likely via a σ-allyl complex[7,17,18] The results obtained for **1a** and **1b** indicate that the *cis*-migration is a very favored process in the lactonic (allyl)palladium intermediates.

These stereocontrolled lactonization reactions should be useful in natural product synthesis. To the best of our knowledge this is the first reported example of a lactonization reaction with a dual stereoselectivity in the addition step. It is interesting to note that the corresponding chlorolactonizations were obtained at a higher chloride concentration (eq. 3). These chlorolactones should be important building blocks since the chloro group



can be substituted by nucleophiles with either inversion or retention.[9] The lactonizations described here offer control of the stereochemistry at three centres in cyclic systems.

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12. The lactone products are very polar and difficult to efficiently extract from aqueous acetic acid.
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14. The coupling constants between the bridgehead protons in **3** and **4** were 7.8 and 7.6 Hz respectively. These values are similar to those observed in analogous *cis*-lactones. Irradiation of the non-allylic bridgehead proton in **4** resulted in a nuclear Overhauser enhancement (NOE) for C*H*-OAc (6%) and C*H*-O-$COCH_2$- (9%). The corresponding irradiation in **3** gave a NOE for C*H*-O-$COCH_2$- (5%) but not for C*H*-OAc (< 1%).
15. It is remarkable that the relative amount of **6** increases on lowering the acetate ion concentration since **6** would be formed via an external *trans*-attack on a π-allyl intermediate.
16. Selected parts of the ^{1}H NMR spectrum of **7**: δ 5.20 (ddd, J=8.0, 6.0, 2.5 Hz, 1H) 4.96 (dd, J=5.0, 3.5 Hz, 1H, CH-O), 4.95 (t, J=8.0 Hz, 1H), 4.83 (dd, J=8.0, 3.5 Hz, 1H). The coupling constant of 5.0 Hz between the bridgehead protons is indicative of a *cis*-lactone.
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