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Regiochemistry of Wacker-Type Oxidation of Vinyl Group in the Presence of Neighboring Oxygen Functions

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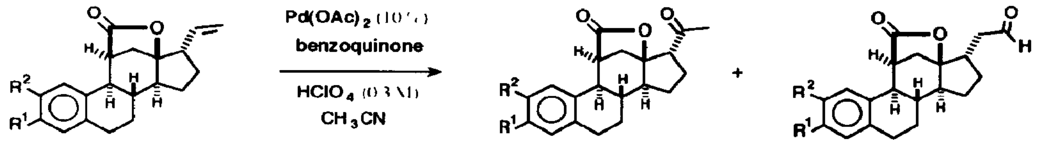
Abstract: Palladium (II) oxidation of (±)-17α-vinyl-1,3,5(10)-estratriene derivatives **1** bearing a lactonic bridge on the β-face affords the expected acetyl derivatives. In contrast, when the lactonic bridge or a hydroxy group is present in the α-face (syn relationship), aldehydes resulting of an anti-Markovnikov hydration are obtained in appreciate yields.

The palladium (II) oxidation of terminal olefins to give methyl ketones (Wacker process) is well established both as an industrial and an organic synthetic reaction.[1] This reaction appears to involve Markovnikov hydration of the complexed double bond followed by oxidation in a one step conversion to methyl ketones.[2] Thus, terminal olefins can be regarded as masked methyl ketones.

In a previous paper, we reported a five step synthesis of (±)-17-vinyl-1,3,5(10)-estratriene derivatives from 1,3-butadiene.[3,4] As an extension of this work, we considered the possibility to unmask the vinyl group by catalytic oxidation. Palladium catalyzed oxidation gave unsatisfactory results when cuprous chloride and oxygen were used as co-reagents.[5] Fortunately, palladium acetate-benzoquinone oxidation, performed in presence of perchloric acid,[6] provided a convenient route to oxidized compounds.



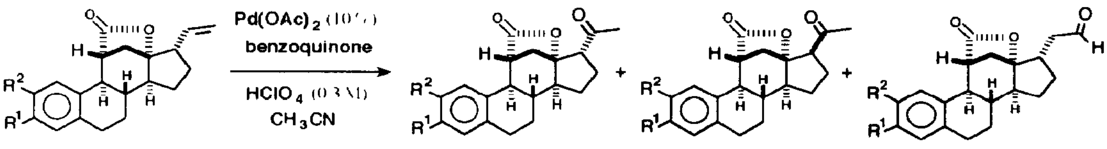
1a, $R^1 = R^2 = H$
1b, $R^1 = R^2 = OMe$

2a, 85 % yield
2b, 79 % yield

3a, 7 % yield
3b, 14 % yield

As expected, treatment of (±)-17α-vinyl-1,3,5(10)-estratriene derivatives **1**, bearing a lactonic bridge on the β-face, afforded the (±)-17α-acetyl-1,3,5(10)-estratriene derivatives **2** in good yields. However, minor amounts of the unexpected terminal aldehydes **3** were obtained besides ketones **2**.[7]

In marked contrast, oxidation of the isomeric (±)-17α-vinyl-1,3,5(10)-estratriene derivatives **4**, bearing a lactonic bridge on the α-face, afforded a mixture of methyl ketone derivatives (expected α-acetyl compounds **5** and epimerized β-acetyl compounds **6**) and aldehydes **7**.



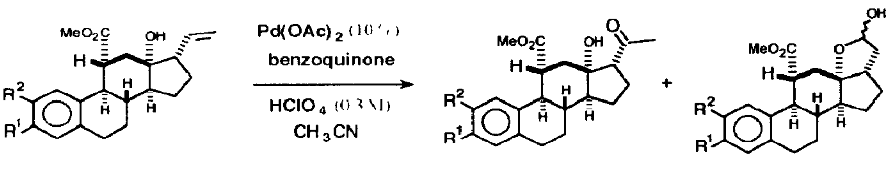
4a, $R^1 = R^2 = H$
4b, $R^1 = R^2 = OMe$

5a, 35 % yield
5b, 39 % yield

6a, 10 % yield
6b, 14 % yield

7a, 34 % yield
7b, 38 % yield

Similarly, lactols **10** were obtained from the (±)-11α-carbomethoxy-13α-hydroxy-17α-vinyl-1,3,5(10)-estratriene derivatives **8** along with the expected ketones **9**.

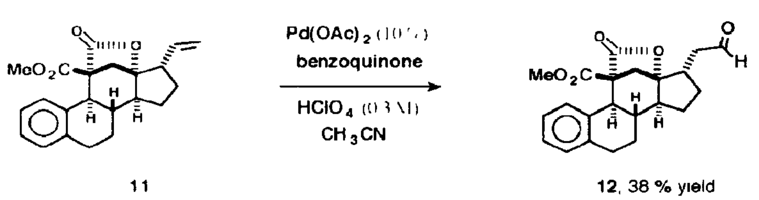


8a, $R^1 = R^2 = H$
8b, $R^1 = R^2 = OMe$

9a, 55 % yield
9b, 54 % yield

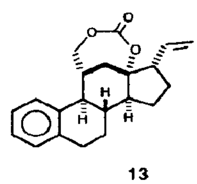
10a, 37 % yield
10b, 38 % yield

Moreover, aldehyde **12** is even the only product we obtained, however with only 38 % yield, from (±)-11β-carbomethoxy-17α-vinyl-1,3,5(10)-estratriene derivative **11** that displays a lactonic bridge on the α-face. Finally, (±)-11α-hydroxymethyl-13α-hydroxy-17α-vinyl-1,3,5(10)-estratriene derivative **13** was recovered unchanged even after 2 h under the same oxidative conditions.



11

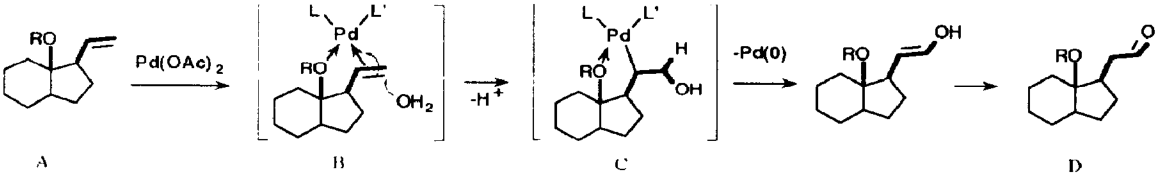
12, 38 % yield



13

Only few reports invoked aldehyde or acetal formations in the course of palladium-catalyzed oxidation of vinyl group.[8,9] In most cases, the anti-Markovnikov addition reaction occurs due to the presence of an heteroatom.[10] The anomalous reaction was explained by postulating that palladium coordinates to the heteroatom and thereby influences the regioselectivity of the hydration step.[11,12] In a previous work, the coordination of a bimetallic complex (palladium, copper) with the heteroatom was even proposed in order to explain the stereoselectivity of the reaction.[13] However, all these examples deal with open chain compounds and no clear correlation between the relative position of the heteroatom and the double bond and the regiochemical outcome of the reaction was established. Although, in our case, the lack of copper reagent excludes the formation of a bimetallic complex, our results clearly show that the coordination of oxygen atom of compounds **4** and **8** with palladium must be nevertheless an important factor in the regioselectivity of the oxidation process.

Thus, the following explanation can account for the regiochemistry we observed when oxidizing **4** and **8** which both display an oxygen atom syn to the vinyl moiety (as in **A**). Addition of palladium acetate leads to the formation of five membered ring palladium complex **B**.[11] **B** then undergoes anti-Markovnikov water addition and yields **C**, an σ-alkylpalladium specie, which upon β-elimination, affords aldehyde **D**.[14]



Acknowledgment. We are indebted to Dr R. Faure for his assistance in NMR measurements.

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7. To a solution of 0.1 mmol of palladium acetate (22.4 mg, 0.1 equiv) and 0.5 mmol of benzoquinone (0.54 g, 0.5 equiv) in 10 mL of acetonitrile, 3.1 mL of water and 0.65 mL of perchloric acid (70 %) were successively added. The mixture was stirred 0.5 h at 20 °C under argon. Then a solution of the steroid derivative (1 mmol) in 12 mL of acetonitrile was added and stirred at 20 °C (0.5 h for **8**, 1.5 h for **1**, **4** and **11**, 2 h for **13**). The mixture was pourred in diethyl ether and washed with a solution of soda (30 %). The aqueous layer was extracted with ether. The combined organic layers were dried over magnesium sulfate, filtrated and concentrated under vacuum. The crude product was purified by chromatography on silica gel.

8. 4-Vinylcylohexene yields minor amounts of the terminal aldehyde besides the expected methyl ketone, see 1b.
9. (a) Aldehydes are the major products of the catalytic oxidation of 1-alkenes with air using a catalyst that comprises $(MeCN)_2PdClNO_2$, $CuCl_2$ and a tertiary alcohol, see: Feringa, B.L. *J. Chem. Soc., Chem. Comm.* **1986**, 909-910. (b) 3-substituted 1-alken-4-ols were oxidized with $PdCl_2$-benzoquinone to afford γ-butyrolactols, see: Nogami, J.; Ogawa, H.; Miyamoto, S.; Mandai, T.; Wakabayashi, S.; Tsuji, J *Tetrahedron Lett.* **1988**, *29*, 5181. (c) Treatment of *N*-allylamides and lactams with O_2 in the presence of $(MeCN)_2PdClNO_2$, CuCl catalyst in anhydrous dichloroethane containing hexamethylphosphoric triamide gives the corresponding aldehydes, while methyl ketones become the major products in the presence of water, see: Hosokawa, T.; Aoki, S.; Takano, M.; Nakahira, T.; Yoshida, Y.; Murahashi, S.-I. *J. Chem Soc., Chem. Comm.* **1991**, 1559-1560. (d) Treatment of terminal olefins bearing electron-withdrawing group with diols in the presence of $PdCl_2$-CuCl-O_2 gives cyclic acetals, see: Hosokawa, T.; Ohta, T.; Murahashi, S.-I. *J. Chem. Soc., Chem. Comm.* **1983**, 848-849. (e) Oxidation of allylamines by the Wacker process, using Li_2PdCl_2, $CuCl_2$ afforded acetals, see: Lai, J.-y.; Shi, X.-x.; Dai, L.-x. *J. Org. Chem.* **1992**, *57*, 3485-3487.
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12. In contrast, the presence of a cyclic acetal in a 1-alkene compound retards the oxidation by coordination, see 1b. Hydroxylation of acrolein acetal with water was unable to be observed, see: Hosokawa, T.; Shinohara, T.; Ooka, Y.; Murahashi, S.-I. *Chem. Lett.* **1989**, 2001-2004.
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