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SYNTHESIS OF CYCLOPENTANOL DERIVATIVES VIA PALLADIUM-CATALYZED CYCLIC ALLYLMETALLATION-DEHYDROMETALLATION[1]

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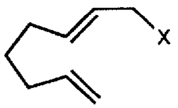
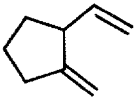
SUMMARY: Treatment of 4-organyl-4-hydroxy-2,7-octadienyl acetate derivatives, i.e., **8**, **10**, **12**, **14**, and **16** with 3 mol % of Pd(PPh$_3$)$_4$ in refluxing MeCN provides in good yields the corresponding cyclopentanol derivatives, i.e., **9**, **11**, **13**, **15**, and **17**, as mixtures of two diastereomers, the major isomers being those in which the hydroxyl and vinyl groups are cis to each other.

As part of our ongoing project on carbometallation,[2] we became interested in allylmetallation[3] involving palladium which, in principle, can proceed via either a four-centered or a six-centered (metallo-ene) process. We specifically hoped to develop cyclization processes involving cyclic carbopalladation[4] of allylic derivatives.[5] To this end 2,7-octadienyl derivatives(**1**) containing Cl, Br, and OAc were prepared, and their cyclization was attempted using various Pd complexes, such as Pd(PPh$_3$)$_4$, Cl$_2$Pd(PPh$_3$)$_2$, Pd(dba)$_2$, and Pd(OAc)$_2$, as catalysts in the presence of a base, such as NEt$_3$ and K$_2$CO$_3$, in various solvents, such as THF, MeCN, benzene, CHCl$_3$, t-BuOH, and DMF.[6] Although the results were condition dependent, there was no indication for the formation of the expected cyclization product **2**, the major side reactions being the well-documented 1,4-elimination to produce 1,3,7-octatriene and allylic rearrangement.[7] To see if the desired cyclic allylpalladation can be observed by blocking the undesirable 1,4-elimination, **3-6** were prepared and heated in refluxing MeCN in the presence of 3 mol % of Pd(PPh$_3$)$_4$. The only observable reaction was allylic rearrangement of **3** to give **7**. In the other cases the starting materials remained unchanged to the extent of at least 90%.



1 (X = Cl,Br,OAc)



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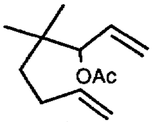

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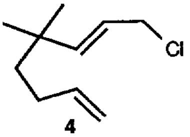

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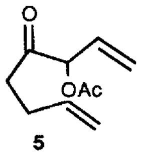

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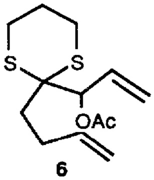

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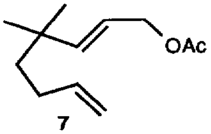
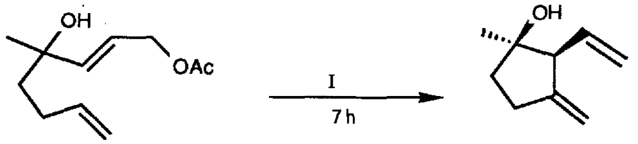


7

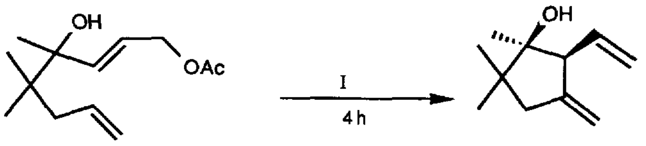
In marked contrast with the above results, treatment of **8** under the same conditions as above for 7 h produced the desired cyclization product **9** in 75% isolated yield (94% by GLC) as a 4:1 mixture of the Z and E isomers (**9a** and **9b**) (eq 1). Interestingly, the corresponding reaction of **10** provided **11** in 82% yield in a highly stereoselective manner (94% Z) (eq 2). As the results shown in eqs 1-5 indicate, the reaction appears to be predictably satisfactory provided that the substrate is an appropriate derivative containing the 4-organyl-4-hydroxy-2,7-octadienyl acetate moiety. Thus, **12**, **14**, and **16** were converted into **13** (80%), **15** (75%), and **17** (73%), respectively, in the yields shown in parentheses. The required starting compounds were prepared from the corresponding ketones by treatment with the dilithio derivative of propargyl alcohol[8] followed by reduction with $LiAlH_4$[9] and acetylation with NaOAc and Ac_2O (eq 6). The Z isomer of **14** was obtained by column chromatographic separation of the minor E isomer. On the other hand, **16** was obtained as a 1:1 diastereomeric mixture and used as such.

The Pd-catalyzed cyclization was carried out by refluxing the hydroxyallyl acetates in dry, deoxygenated MeCN in the presence of 3 mol % of $Pd(PPh_3)_4$. The stereochemical assignments have been made primarily by a combination of ^1H and ^{13}C NMR chemical shifts evaluation and ^1H 2D NOESY NMR analysis. In all cases the major stereoisomer or one of the major stereoisomers is that in which the vinyl group on the cyclopentane ring and the hydroxy group are cis to each other. This can be rationalized by invoking chelation between Pd and OH, e.g., **18**, in the presumed palladium-ene process. The minor isomer of **13** is the one in which the hydroxy group is cis to the vinyl group and trans to the allyl group. Only traces, if any, of the other possible isomers were formed. Consideration of molecular models indicates that the (R,S) or (S,R) isomer of **16** can readily cyclize only from the conformation in which Pd is proximal to the hydroxy group, e.g., **19** to give **17a**. The (R,R) or (S,S) isomer, on the other hand, can readily cyclize only from the conformation in which Pd is proximal to the methyl group, i.e., **20**, to produce **17b**. The endo stereochemistry of the vinyl group is in agreement with the above prediction. In this case, however, two other minor isomers were also formed in 11 and 3% yields (GLC and ^{13}C NMR).



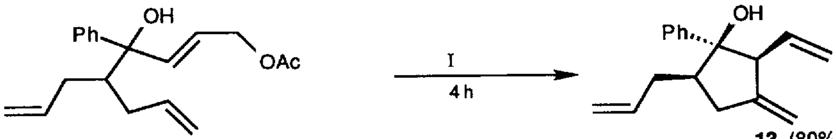
(1)

8 **9** (75%, Z/E = 4/1)



(2)

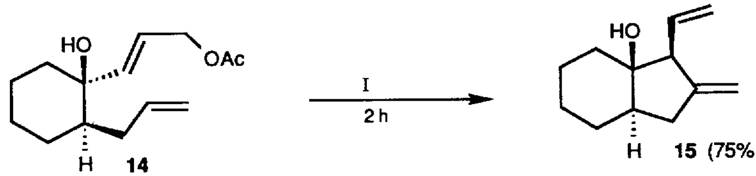
10 **11** (82%, Z/E = 15/1)



12

13 (80%, $\underline{Z}/\underline{E}$ = 1.4/1)

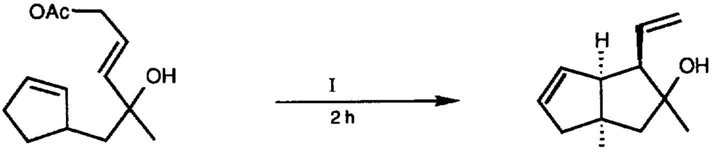
(3)



14

15 (75%, $\underline{Z}/\underline{E}$ = 1.3/1)

(4)

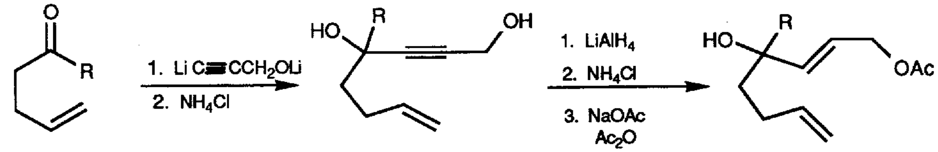


16

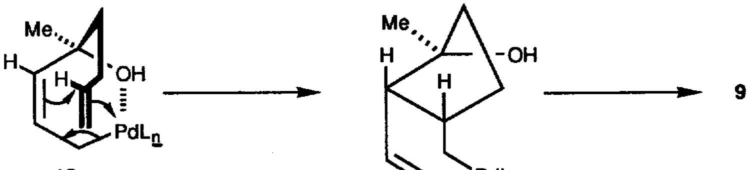
17 (73%, $\underline{Z}/\underline{E}$ = 1/1)

(5)

I = 3 mol % $Pd(PPh_3)_4$, MeCN, reflux
Only the stereochemistry of the major isomer is shown.



(6)



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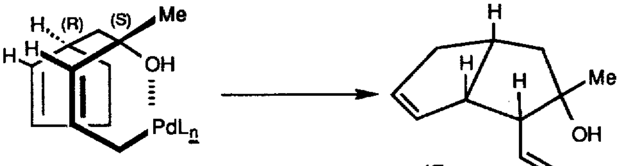
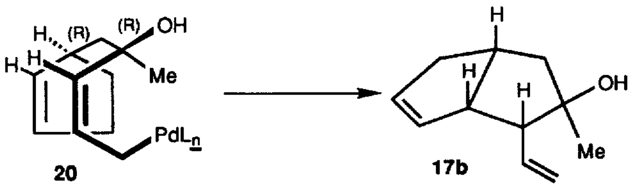
(7)



19

17a

(8)



20

17b

(9)

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(6) One solvent we did not consider initially was HOAc which was used by Oppolzer and his coworkers.[5] During the course of our study we became aware of their work. Although the completion of our work was delayed due to the premature departure of S. Iyer, the crucial findings using MeCN as a solvent had been made prior to the publication of ref. 5.

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