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α,β-Epoxy Vinyl Triflates in Pd-Catalyzed Reactions

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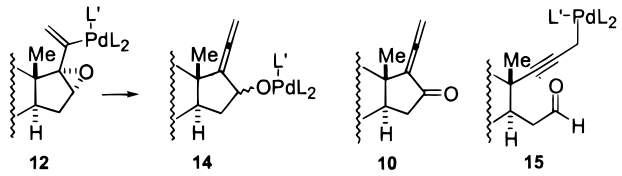
ABSTRACT

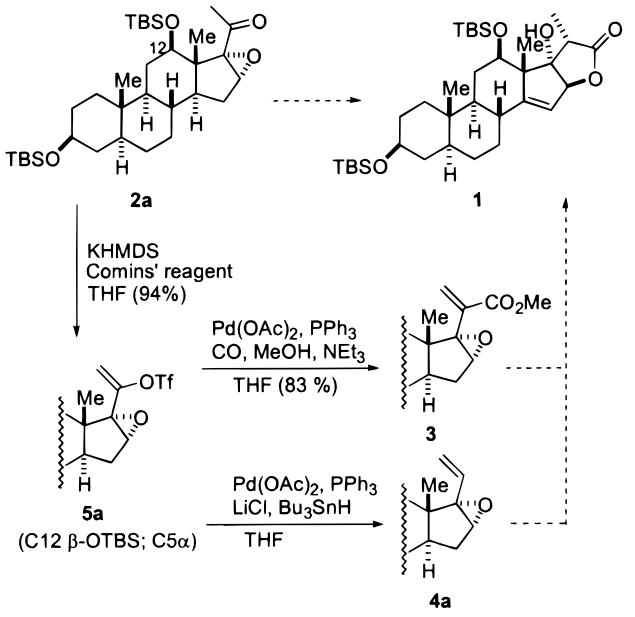


Reactions of steroidal α,β-epoxy vinyl triflates in Pd-catalyzed reactions are described. Oxidative insertion of Pd^0 into the C–O bond, giving vinylpalladium 12, is faster than formation of the π-allyl derivative from the vinyl epoxide. Although 12 can be trapped under certain conditions, it eventually rearranges to palladium alkoxide 14, which is in equilibrium with 15 and/or 10.

As part of a project directed toward the synthesis of cephalostatins,[1] we wanted to prepare lactone **1** from epoxide **2a** (Scheme 1).[2] Lactone **1** can be envisioned to arise from either **3** or **4a**. To this end, triflate **5a** appeared to be an attractive intermediate since it would allow access to both compounds by Pd-mediated carbonylation or reduction.[3]

Conversion of **2a** to vinyl triflate **5a** was achieved by the use of Comins' procedure.[4] Triflate **5a** possesses two possible sites for reaction with Pd^0 (insertion into either the vinyl triflate C−O bond or the allyl epoxide C−O bond), and it was uncertain which functionality would be more reactive.[5] In addition, the desired products (**3** or **4a**) could also undergo Pd^0 insertion to give π-allylpalladium complexes. However, in any event, it was found that carbonylation of **5a** provides ester **3** in good yield.[6]

Scheme 1



(1) Petit, G. R. Y.; Williams, M. D.; Boyd, M. M. R. *J. Nat. Prod.* **1998**, *61*, 953 and references therein.

(2) Epoxide **2a** was synthesized from the commercially available steroid, hecogenin in seven steps. The detailed experimental procedure is shown in the Supporting Information.

(3) Methods for the Pd-mediated reduction: (a) With Et_3SiH, Kotsuki, H.; Datta, P. K.; Hayakawa, H.; Suenaga, H. *Synthesis* **1995**, 1349. (b) With Bu_3N/HCO_2H, Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1984**, *25*, 42, 4821. (c) With Bu_3SnH, see ref 7. (d) With Et_2NH/BH_3, Lipshutz, B, H,; Buzard, D. J.; Vivian, W. *Tetrahedron Lett.* **1999**, *40*, 6871.

(4) (a) Comins, D. L.; Dehghani, A.; Foti, C. J.; Joseph, S. P. *Org. Synth.* **1997**, *74*, 77. (b) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299.

(5) It was reported that in the case of 1-acetoxy-2-bromo-2-alkenes, the bromo substituent dramatically reduces the reactivity of the olefin in Pd-catalyzed substitutions, and that coupling between bromoalkenes and terminal alkynes proceeds without side reactions with acetoxy substituents. (a) Nwokogu, G. C. *Tetrahedron Lett.* **1984**, *25*, 31, 3263. (b) Nwokogu, G. C. *J. Org. Chem.* **1985**, *50*, 3900.

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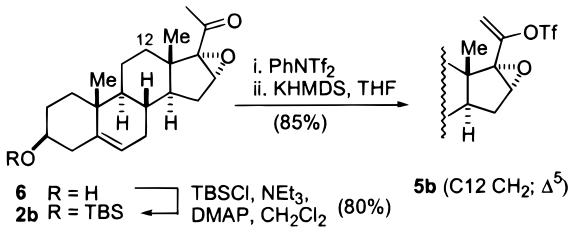
Elaboration of ester **3** to lactone **1** was found to be problematic, and we therefore turned our attention to the alternative route. Initial attempts to reduce the triflate **5a** with Bu_3SnH[7] following Stille's procedure[8] gave a number of products depending on reaction conditions. While we were able to obtain moderate amounts of the desired allyl epoxide **4a**,[9] the interesting structures of other isolated products prompted us to further investigate these reactions. Triflate **5b**, prepared from the known ketone **6**,[10] was also utilized in these studies (Scheme 2).

Scheme 2



Some representative examples of the reactions are shown in Scheme 3. Reaction of **5a** with $Pd(OAc)_2$, PPh_3, LiCl, and 1 equiv of Bu_3SnH gave a mixture of vinyl epoxide **4a** and allenic alcohol **7a** along with recovered starting material[11,12] in a ratio of 4:1:2 (eq 1). Subjecting **5b** to the same reaction conditions also gave the corresponding epoxide **4b**, allenic alcohol **7b**, and starting material, but in a ratio of 2:2:1.[13]

We speculated that **7** might have arisen from allyl epoxide **4** by oxidative addition and subsequent β-elimination. However, resubjecting **4** to the reaction conditions resulted in reduction instead of β-elimination, giving a mixture of homoallyl alcohol **8**[14] and allyl alcohol **9** as a mixture of *E* and *Z* isomers (eq 2).[15]

On the other hand, treatment of **5** with a stoichiometric amount of Pd^0 led to the formation[16] of **7**, but surprisingly, as a mixture of C16 epimers (eq 3).[17] A small amount of allenone **10** was also obtained when **5a** was used in this reaction. These results suggest that allenic alcohol **7** is formed by direct rearrangement of the vinylpalladium intermediate.[18]

(6) Similarly, it was recently reported that Pd-catalyzed carbonylation of 1-acetoxy-2-bromo-2-alkenes proceeds without involvement of the allylic ester. Trost, B. M.; Oslob, J. D. *J. Am. Chem. Soc.* **1999**, *121*, 3057.

(7) Alternative methods gave unsatisfactory results: Et_3SiH procedure[3a] resulted in very low conversion. Bu_3N/HCO_2H procedure[3b] gave a mixture of unidentifiable products, presumably due to acid sensitivity of vinyl epoxide.

(8) (a) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033. For leading references for the Stille reaction, see (b) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (c) Farina, V.; Krishnamurthy, V.; Scott, W. J. *The Stille Reaction*; John Wiley and Sons, Inc.: New York, 1998.

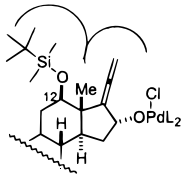
(9) Because of the difficulty in separation from starting material, **4a** was not isolated in most cases. An alternative way to make this compound is described in the Supporting Information.

(10) (a) Julian, P. L.; Meyer, E. W.; Ryden, I. *J. Am. Chem. Soc.* **1950**, *72*, 367. (b) Julian, P. L.; Karpel, W. J. *J. Am. Chem. Soc.* **1950**, *72*, 362. (c) Julian, P. L.; Meyer, E. W.; Karpel, W. J.; Waller, I. R. *J. Am. Chem. Soc.* **1950**, *72*, 5145.

(11) This reaction does not go to completion with 1 equiv of Bu_3SnH. It is known that triorganostannyl hydrides are converted into ditins by Pd catalyst,[12] although Pd-catalyzed reduction has also been described. In our case, addition of more than 1 equiv of the hydride resulted in a mixture of products resulting from over-reduction of the allyl epoxide, along with **4**, **7**, and **5**. Addition of additional Pd catalyst had no effect on the reaction.

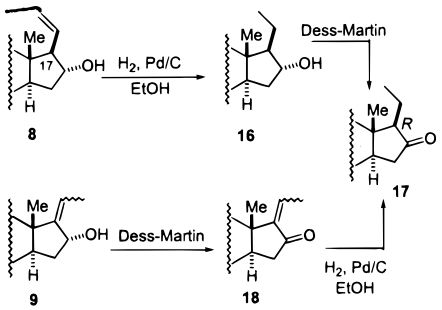
(12) Mitchell, T. N. *Synthesis* **1992**, *9*, 803.

(13) It is speculated that the steric repulsion between C12 TBS group of **14a** suppresses its formation, resulting in the lower ratio.

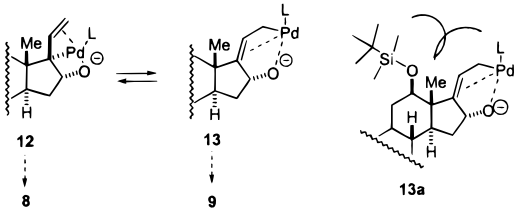


14a

(14) The C17 configuration of the homoallyl alcohol **8a** was determined as follows. Hydrogenation of **8a** gave saturated alcohol **16**, which was oxidized to ketone **17**. Allyl alcohol **9a** was oxidized to enone **18**, which was hydrogenated to obtain **17**. Since it is known that the $\Delta^{17(20)}$ olefin in steroids is hydrogenated from the α-face, the C17 configuration in **17** is *R*, as shown.

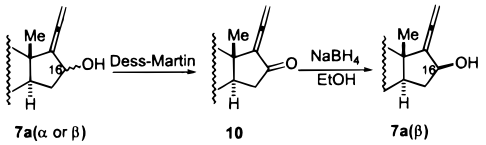


(15) The high regioselectivity in the reduction of **4a** compared to **4b** can be explained by the relative stability of the isomeric π-allyl palladium species in each case. It is likely that **13** is more stable than **12** because of less steric repulsion between the steroidal core. However, sterics between Pd ligand and bulky TBS protecting group at C12 (see **13a**) could invert the relative stability. Transmetalation and reductive elimination gives the reduced compounds, of which the ratio should reflect the energy difference between **12** and **13**.



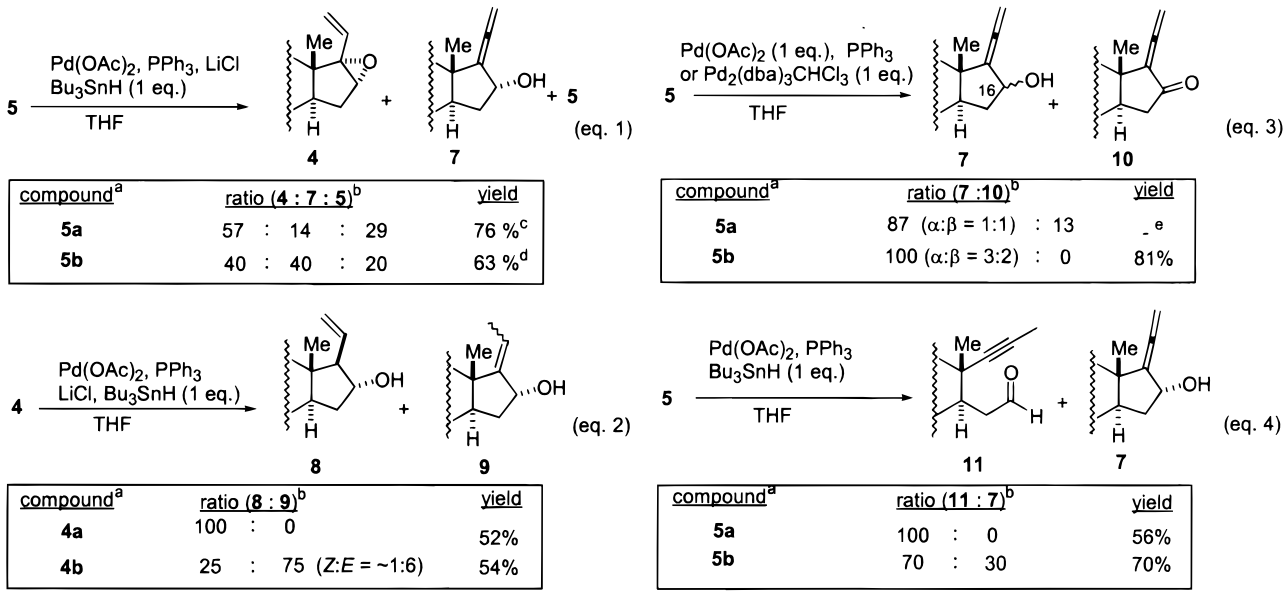
(16) Addition of LiCl resulted in no reaction, presumably because of the stablization of Pd^{II} by chloride. Tsuji, J. *Palladium Reagents and Catalysis, Innovations in Organic Synthesis*; John Wiley and Sons, Inc.: New York, 1995; pp 19−20.

(17) To determine the stereochemistry of isomeric alcohols **7a**, the mixture of isomers was oxidized to allenone **14** and reduced with $NaBH_4$. It is assumed that the major isomer is the one with the β-configuration at C16, **7a**.



(18) It is also possible that vinylpalladium species transmetalates with $(Bu_3Sn)_2$ (generated from 2 equiv of Bu_3SnH)[12] to give vinyltin species before the rearrangement. However, the use of $(Bu_3Sn)_2$ in place of Bu_3SnH gave different products depending on substrates.

Scheme 3



compound[a]	ratio (4 : 7 : 5)[b]	yield
5a	57 : 14 : 29	76 %[c]
5b	40 : 40 : 20	63 %[d]

compound[a]	ratio (7 :10)[b]	yield
5a	87 (α:β = 1:1) : 13	-[e]
5b	100 (α:β = 3:2) : 0	81%

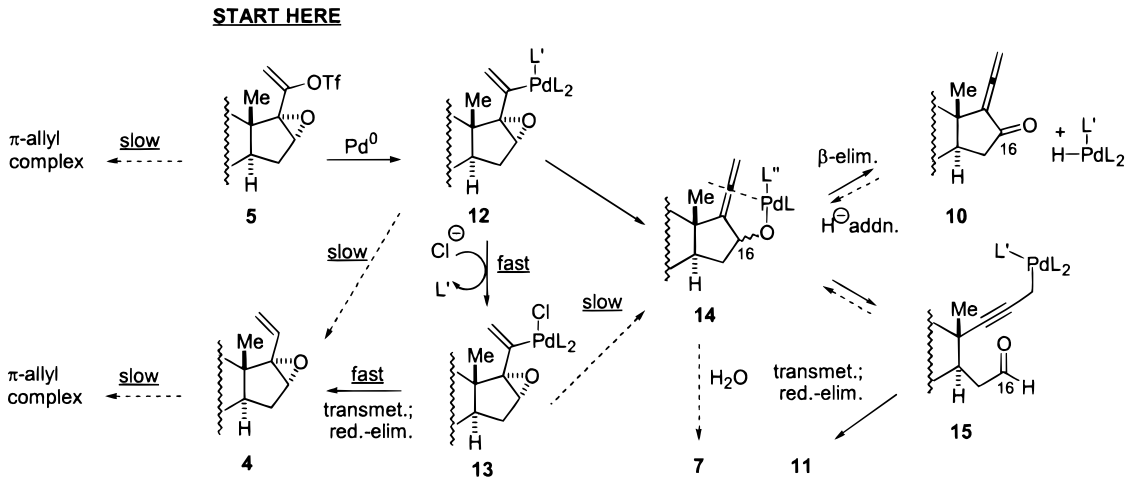
compound[a]	ratio (8 : 9)[b]	yield
4a	100 : 0	52%
4b	25 : 75 (*Z*:*E* = ~1:6)	54%

compound[a]	ratio (11 : 7)[b]	yield
5a	100 : 0	56%
5b	70 : 30	70%

[a] **a**: C12 β-*tert*-butyldimethylsilyloxy C5α **b**: C12 CH_2; Δ^5 [b] Determined by ^{1}H-NMR
[c] 76% as a mixture of **5a** and **4a** [d] 63% combined yield of **4b** and **7b** [e] Not determined because of inseparable impurities
[f] 70% combined yield of **11b** and **7b**

When **5** was subjected to salt-free conditions, the steroidal D ring fragmented to give aldehyde **11** along with trace of **7** (eq 4). Overall, this reaction (from epoxy-ketone to alkyne-aldehyde) is equivalent to Eschenmoser's fragmentation.[19]

The foregoing experimental results can be explained as follows (Figure 1). As mentioned, there are three possible reactive sites (vinyl triflate of **5** or allyl epoxide of **4** and **5**) for Pd^0 under these conditions. However, oxidative addition to the vinyl triflate moiety proceeds faster than that of vinyl epoxides.[6] Presumably, in the presence of LiCl, **12** quickly exchanges ligand to give **13**.[20] The transmetalation step then becomes relatively faster than the rearrangement,[21] resulting in predominant formation of **4** upon reductive elimination (eq 1). Under salt-free conditions (eq 4), the transmetalation proceeds slower and rearrangement to alkoxide **14** becomes competitive. It is of note that carbonylation of **5a** (Scheme



L' = OTf or solvent; L" = OTf, solvent or Cl
[a] The Pd is charged in the case if coordinated with solvent

Figure 1.

1) under salt-free conditions gave no rearrangement, indicating that CO migratory insertion also proceeds faster than the rearrangement.[22]

The mechanism for the C16 epimerization in eq 3 is unclear. One possibility is that Pd alkoxide **14** undergoes β-elimination to give allenone **10**.[23] Readdition of the palladium hydride[24] from the α-face of the C16 ketone would result in overall epimerization of this stereocenter. The isolation of a small amount of **10** supports this idea. Alternatively, **14** might be in equilibrium with ring-fragmented intermediate **15**, formed either by inter- or intramolecular coordination of Pd^{II}. This could close back[25−27] from either face of the aldehyde, resulting in overall epimerization at C16. This mechanism is also attractive since isolation of **11** can be explained. It is possible that both pathways operate competitively.[28] With **5a**, it is likely that the ring-fragmentation route would be disfavored because the TBS protecting group at C12 would hinder the coordination of Pd^{II} with the allene. The major pathway for this substrate would then likely be the allenone-pathway, which could explain the isolation of **10** from this substrate.

To summarize, it was shown that oxidative addition of Pd^0 to the vinyl triflate in **5** is faster than that to the vinyl epoxide, in accordance with a previous report with a related substrate.[6] The resulting vinylpalladium **12** can be trapped if the subsequent step is faster than rearrangement (i.e., carbonylation or transmetalation in the presence of chloride ligand). However, it eventually rearranges to alkoxide **14**, which is in equilibrium with **10** or **15**.

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Supporting Information Available: Experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) (a) Tanabe, M.; Crowe, D. F.; Dehn, R. L. *Tetrahedron Lett.* **1967**, *40*, 3943. (b) Muller, R. K.; Felix, D.; Schreiber, J.; Eschenmoser, A. *Helv. Chim. Acta* **1970**, *53*, 1479.

(20) Farina, V.; Krishnan, B.; Marshall, D. R.; Roth, G. P. *J. Org. Chem.* **1993**, *58*, 5434.

(21) It was originally reported that LiCl is required in the Stille reaction for vinyl or aryl sulfonates.[8a] However, it was later found that the effect of LiCl is more complicated and sensitive to ligands and solvents.[8c]

(22) It has been recognized that the rate-limiting step for the Stille reaction is the transmetalation step, whereas that for carbonylation is oxidative addition.[8c]

(23) For β-elimination of Pd−methoxide to form "Pd−H", (a) Grushin, V. V. *Chem. Rev.* **1996**, *96*, 2011. (b) Elsevier: C. J.; Toth, I. *Organometallics* **1994**, *13*, 2118. (c) Milstein, D.; Frolow, F.; Portnoy, M. *Organometallics* **1991**, *10*, 3960. (d) Milstein, D.; Portnoy, M. *Organometallics* **1994**, *13*, 600.

(24) Although "Pd−H" insertion into CO, CO_2, and CS_2 are well documented,[23a] the corresponding reaction with aldehydes is not precedented.

(25) While allyl- or propargylpalladium species are electrophilic in nature,[26] corresponding nickel species are known to react with aldehydes.[27] We therefore speculate that the intramolecular version of this transformation may be possible.

(26) A bis-π-allylpalladium species was reported to have a nucleophilic character: (a) Nakamura, H.; Asao, N.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1995**, 1273. (b) Nakamura, H.; Shim, J. G.; Yamamoto, Y. *J. Am. Chem. Soc.* **1997**, *119*, 8113.

(27) Hegedus, L. S. *Transition Metals in the Synthesis of Complex Organic Molecules*; University Science Books: California, 1994; p 320.

(28) When the reaction is carried out with stoichiometric amount of Pd^0, **11** is not formed (Scheme 3, eq 3). This observation might be due to a stable bidentate chelate of **14** that does not readily undergo transmetalation with Bu_3SnH.