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The Effect of Tether Substituents on the Selectivity of Pd Catalyzed Enyne Cyclizations. A Total Synthesis of Chokol C

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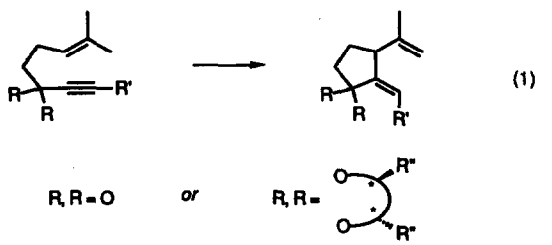
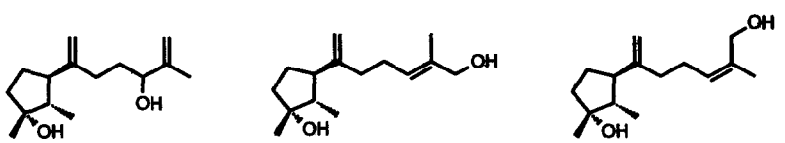
Summary: In the context of the palladium catalyzed cycloisomerization of enynes, two of the most important tether substituents, the carbonyl group because of its general synthetic versatility and the ketal because of its prospect to induce absolute stereochemistry by employing the ketal from a chiral diol, are probed within the context of a synthesis of chokol C, an antifungal compound produced by *Phleum pratense* when infected by a pathogenic fungus *Epichloe typhina*.

To probe the potential synthetic power of a palladium catalyzed cycloisomerization of enynes (eq. 1),[1] we have undertaken a study of the effect of tether substituents on the chemo-, regio-, diastereo- and enantioselectivity as well as rate of the reaction. Two structural features of particular interest are the carbonyl group and its corresponding ketal because of the general synthetic versatility of the former and the prospect of the latter to induce absolute stereochemistry via a ketal derived from a chiral diol.[2] The discovery of the



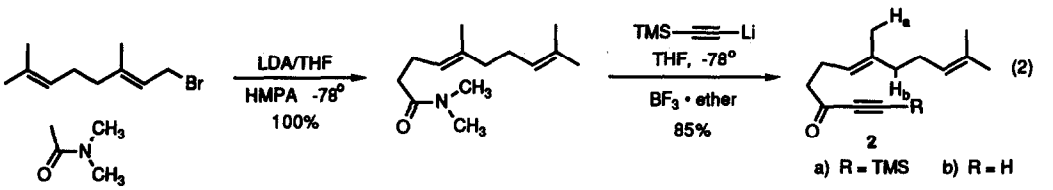
(1)

chokols, antifungal compounds isolated from the stromata of the timothy plant *Phleum pratense* when infected by a pathogenic fungus *Epichloe typhina*[3] provides an excellent framework within which to explore these substituent effects. While syntheses of chokols A[4] and G[5] have been reported, no syntheses of the most active members chokols B, C, and D have appeared which induced us to focus on chokol C (**1**) but in a format that may give access to all three.



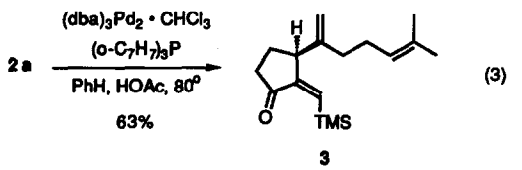
CHOKOL B CHOKOL C (1) CHOKOL D

Eq. 2 illustrates the simplicity with which the requisite substrate **2**[6] for the palladium catalyzed cycloisomerizations is available in two steps from commercially available materials. It is interesting to



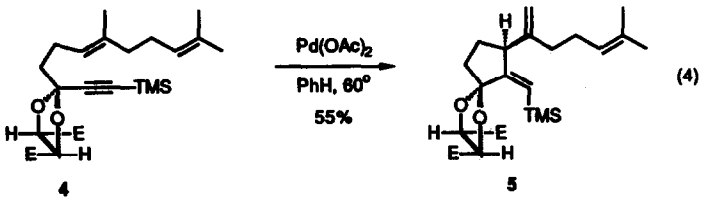
note the efficiency of the ketone synthesis with the simple dimethylamide *provided that a protic or Lewis acid is added to the reaction mixture prior to quenching with water.* In the absence of such acids to protonate or coordinate nitrogen of the tetrahedral intermediate, it preferentially collapses to return starting materials!

Earlier attempts to cycloisomerize an ynone analogous to **2b** failed[7] as did an attempt to cycloisomerize **2b**. Two effects may account for these failures - 1) the 120° bond angle of an sp^2 carbon in the tether or 2) an extraordinarily high reactivity of the acetylenic proton towards palladium. We therefore examined the cycloisomerization of **2a** to differentiate between these two rationales. While choice of ligand appears important (i.e., electron rich and non-bulky ligands like N,N'-bisbenzylideneethylenediamine, triphenylphosphine, and dppp give poor results), tri-o-tolylphosphine, a common ligand for this reaction,[1,8] under the conditions outlined in eq. 3 proved highly effective. The strong activating effect of the carbonyl



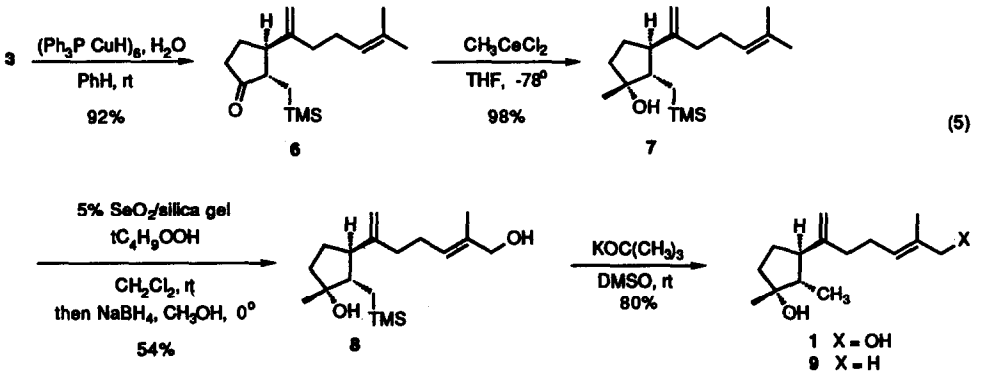
group is apparent from the lack of rate inhibition normally experienced in the Pd catalyzed cycloisomerization by placing a TMS group on the acetylenic carbon. It is important to note the regioselectivity of this cycloisomerization since migration of either allylic hydrogen H_a or H_b of the enyne **2a** (eq. 2) to give **3** or a double bond isomer respectively is feasible. Thermal Alder ene reactions normally lead only to migration of H_b.[9] In this palladium catalyzed reaction, only H_a migrates since **3**[6] is the exclusive product.

Prospects for asymmetric induction in this cycloisomerization were probed by studies of the chiral ketal **4** derived from ketone **2a** and diethyl tartrate as a simple cheap chiral auxillary. The presence of the acetylenic TMS group but the absence of the carbonyl group activation in **4** creates a substrate that requires the employment of a ligandless catalyst, palladium acetate (eq. 4). Again, only a single regioisomeric product **5**[6] formed. Thus, tether substituents do not influence this issue of regioselectivity of allylic hydrogen migration. Most importantly, the ^1H nmr spectrum revealed a diastereomer ratio of 8.5:1. Hydrolysis of the ketal (HCl, H_2O, CH_3OH, 40°) generates the ketone **3**, $[\alpha]_D$ -30.0° (c 0.05, C_2H_5OH).



(4)

The acceptability of a ketone functionality, the high diastereoselectivity with the corresponding ketal using an economical chiral auxillary, and the extraordinary regioselectivity of the cycloisomerization independent of the nature of the tether greatly enhance the scope and potential of this synthetic method. To demonstrate this point, the synthesis of chokol C was completed as outlined in eq. 5. The E/Z ratio of 10:1 of



(5)

6[6] obtained by conjugate reduction[10] corresponds to the thermodynamic ratio which was established by independent equilibration. As found previously,[4c,5a] methylcerium dichloride proved most diastereoselective in producing epimer 7[6] (8:1). The chemoselectivity of the allylic oxidation[11] of 7[6] is extraordinary and presumably reflects the electrophilic nature of the selenium dioxide oxidation.[12] Chokol C (**1**) is obtained in 19% overall yield in seven steps from commerically available materials. Deoxychokol C **9** obtained by desilylation of **7** [$KOC(CH_3)_3$, DMSO, rt] which, in turn, derived from the tartrate ketal **5** has $[\alpha]_D$ -32.6° (c 0.05, C_2H_5OH) {cf chokol C lit.[3] $[\alpha]_D$ -32.0° (c 0.25, C_2H_5OH)} which suggests the absolute configuration induced in eq. 4 corresponds to the configuration of the natural product. If we assume, the intramolecular carbametalation has a late transition state, molecular modelling of **5** and its C(3) epimer may provide insight into this selectivity. Indeed, forcefield calculations show **5** to be 1.0 kcal/mol more stable than its C(3) epimer which largely results from interactions of the TMS group with the proximal carboethoxy group of the tartrate ketal. Thus, the TMS group serves as both a chemo- and diastereoselectivity control element in Pd catalyzed enyne cyclizations. The late intermediate **7** should also provide entry to chokols B and D by variation of the allylic oxidation protocol.

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