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Catalytic Palladium-Mediated Tetraene Carbocyclizations: The Efficient Stereochemical Control of Newly Formed Methyl-Bearing Stereocenters

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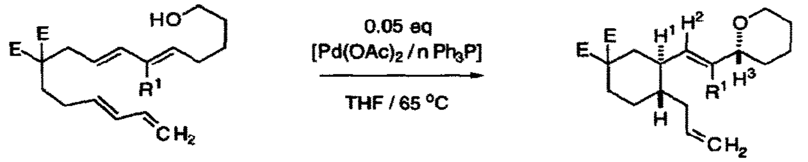
Summary: Certain tetraene substrates bearing a trisubstituted double bond as part of one of the diene subunits undergo palladium-catalyzed cascade cyclization to afford cyclized products in which a new methyl-bearing stereocenter is generated in a stereoselective fashion.

In recent studies we established the viability of a novel palladium-catalyzed cascade cyclization reaction that effects the construction of two rings with control of their 1,4-relative stereochemistry.[1,2] For example, the acyclic tetraene **1a** undergoes palladium-catalyzed cyclization (0.05 equiv. [$Pd(OAc)_2$ / 3 PPh_3], THF, 65 °C, 12 h) to afford **2a** in good chemical yield (82 %). In preparation for applications in natural product total synthesis, we wondered whether the scope of the methodology would permit the use of more highly substituted diene subunits within the tetraene substrate. Metal-mediated cyclizations that rely on the initial complexation of an alkene or alkyne about a low oxidation state metal center are often sensitive to the presence of additional (particularly electron donating) substituents, and relatively more stringent reaction conditions are required for successful cyclization. This effect was noted in the nickel-catalyzed [4+4]-cycloaddition reactions developed by Wender and co-workers,[3] and is apparent when one compares the reported facility of palladium-catalyzed telomerizations of 1,3-butadiene versus that of substituted 1,3-dienes.[4] We therefore prepared three methyl-substituted tetraene substrates, each bearing the E geometry about the trisubstituted double bond, and examined their palladium-catalyzed cyclizations. By virtue of the additional substituents, these substrates generate additional new methyl-bearing stereocenters in the product, and thereby, give further insight into both the scope and stereoselectivity of this cyclization chemistry.

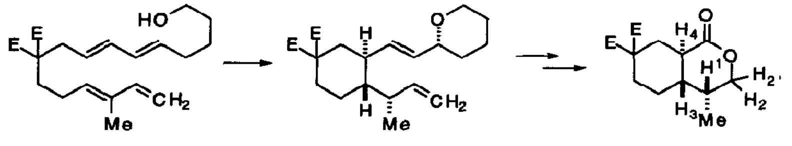


1a $R^1 = H$, $E = CO_2Et$
b $R^1 = Me$, $E = CO_2Et$

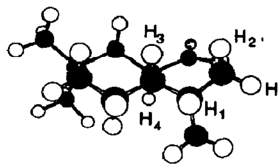
2a $R^1 = H$, $E = CO_2Et$ (82 %)
b $R^1 = Me$, $E = CO_2Et$ (65 %)

The initial attempts at palladium-catalyzed cyclization of tetraene **1b** were rather disappointing. Under the conditions employed for **1a**, only a small percentage reacted and starting material was largely recovered unchanged. However, it is known that coordinately unsaturated palladium catalyst systems turnover faster in Stille coupling reactions,[5] and much to our delight, we find that the use of two, rather than three, equivalents of triphenylphosphine per palladium affords a more active tetraene cyclization catalyst. Tetraene **1b** undergoes smooth cyclization (0.05 equiv. [$Pd(OAc)_2$ / 2 PPh_3], THF, 65 °C, 12 h) affording cyclized product **2b** in 65 % isolated yield and 95 % diastereomeric purity. The remaining 35 % of the mass is isolated as a mixture of isomeric products resulting from the tetraene-to-triene cycloisomerization pathway.[6] The *E*-geometry of the newly formed trisubstituted double bond in **2b** is assigned on the basis of large nOe's (10 %) observed for hydrogens H^1 and H^3 when H^2 is irradiated. It should also be noted that the *E*-geometry is consistent with our working model for the catalytic cycle which assumes transoid η^3-allyl-containing metallacyclic intermediates.[1,2]

The second model substrate is the methyl-substituted tetraene **3**. As in the case of **2b**, attempts to cyclize this substrate using the standard 0.05 equivalents of [$Pd(OAc)_2$ / 3 PPh_3] led to only 10-15 % of the desired cyclization-trapping product. However upon treatment with 0.05 equivalents of the [$Pd(OAc)_2$ / 2 PPh_3] mixture in refluxing THF, tetraene **3** cyclizes to afford the desired product **4** in 65 % yield (97 % diastereomeric purity). The methyl substitution pattern in tetraene **3** leads to the formation of a fourth stereocenter in the cyclized product **4**. Based on the results of deuteration studies described in the preceding paper, we anticipated that this new methyl-bearing center would be generated in a stereochemically controlled fashion. This indeed proves to be the case. Furthermore, the 97 % diastereomeric purity of **4** is among the highest observed to date in these cyclizations, and suggests to us that compared to simple models such as **1a**, the cyclizations of structurally complex tetraenes could generally be more highly stereoselective. It is interesting to note that the same is true in the case of the intramolecular Diels-Alder reaction. Generally the more highly constrained the substrate, the more efficient the cycloaddition. Nonetheless, we find it quite remarkable that the



3 (E = CO_2Et) **4** (E = CO_2Et) **5**



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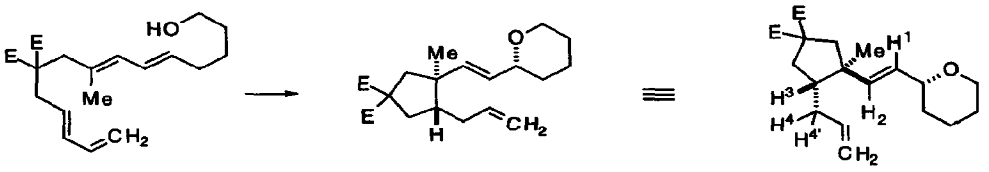
cyclization of an acyclic tetraene generates four new stereocenters in a highly selective fashion, two of which reside exocyclic to the initially formed cyclohexane ring.

The sense of stereocontrol exhibited in the cyclization to **4** is established via conversion to the bicyclic lactone **5**. Selective oxidation of the terminal double bond (cat. OsO_4 / $NaIO_4$) followed by $NaBH_4$ reduction of the aldehyde yields an intermediate alcohol. Ozonolysis (1. O_3, CH_2Cl_2, -78 °C; 2. Me_2S) of the remaining internal double bond affords an intermediate lactol which upon PCC oxidation affords diastereomerically pure **5**. The cis relative stereochemistry of the methyl group and the adjacent ring substituent is assigned on the basis of the near zero H_1-H_3 coupling constant, suggesting H_1's pseudoequatorial disposition. The assignment is confirmed by the observation of a large nOe from the methyl group to H_4 (10 %) and by the lack of a significant nOe from the methyl group to H_3. The three dimensional structure of a relevant fragment of **5**, obtained via molecular modeling (PCModel v 4.3), is shown above (*i.e.*, **6**). The estimated Me-H_4 distance from structure **6** is 2.8 Å; the Me-H_3 distance, 3.5 Å.

To complete this short study on the cyclizations of methyl-substituted diene substrates we prepared tetraene **7**, a substrate for which cyclization would lead to a product possessing a methyl bearing quaternary stereocenter. The stereocontrolled generation of quaternary centers remains a significant synthetic problem in organic synthesis.[7,8] A new solution to this problem via palladium-mediated tetraene cyclization could lead to a novel method for ultimately setting the angular methyl group at the ring fusion of a bicyclic ring system; a common structural element present in a variety of natural products. Upon treatment with 0.05 equivalents of the [$Pd(OAc)_2$ / 2 PPh_3] mixture in THF (65 °C), **7** cyclizes to **8** in 68 % isolated yield (94 % diastereomeric purity). The successful cyclization of **7** demonstrates two important extensions of the methodology: 1) that the formation of a five-membered carbocyclic ring is efficient; and 2) that the formation of the quaternary methyl-bearing stereocenter is accomplished in stereoselective fashion.



7 **8**

The stereochemistry of the cyclopentane ring substituents in **8** is established from the results of nOe studies. Irradiating the methyl group results in a 24 % nOe to H_1 and a 4 % nOe to H_2. This observation defines a preferred solution conformation of **8** that places the methyl and H_2 on opposite faces of the cyclopentane ring, and thereby, affords the opportunity to assign the relative stereochemistry between the two cyclopentane ring stereocenters by comparing the sites and magnitude of nOe's obtained by irradiating the methyl and by irradiating H_2. In addition to the nOe's to H_1 and H_2, irradiating the methyl group exhibits a large (>10 %) nOe at H_4, suggesting that the methyl and H_4 are relatively close in space, and a smaller enhancement (3 %) at $H_{4'}$. Irradiating H_2 shows complementary effects; no nOe at H_4 or $H_{4'}$, but a significant enhancement (4 %) at H_3 suggesting that H_2 and H_3 are on the same face of the ring system. These data, in conjunction with an analysis of three dimensional models for the diastereomers of **8** obtained via molecular modeling, support the structural assignment as illustrated for **8**.

In summary, metal-mediated cyclizations that rely on the initial complexation of an alkene or alkyne about a low oxidation state metal center are often sensitive to the presence of additional (particularly electron donating) substituents, and relatively more stringent reaction conditions are usually required for successful cyclization. However, we find that with minor modification of the standard palladium catalyst system tetraene substrates bearing a trisubstituted double bond as part of one of the diene subunits undergo efficient, diastereoselective cascade cyclization. These cyclization studies establish that: a) a new trisubstituted double bond can be generated in a stereoselective fashion by the cyclization; b) the cyclization can be used to generate a total of two new tetrahedral stereocenters in a stereoselective fashion exocyclic to the newly formed carbocyclic ring; c) five- and six-membered rings can be formed in a stereoselective fashion; and d) a quaternary methyl-bearing stereocenter can be generated in a stereoselective fashion by the cyclization. Further studies and synthetic applications are in progress.

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