Double Palladium(II)-catalyzed Allylic Transpositions. Stereoselective Synthesis of Dihydroxy-(*E*,*Z*,*E*)-conjugated Trienes

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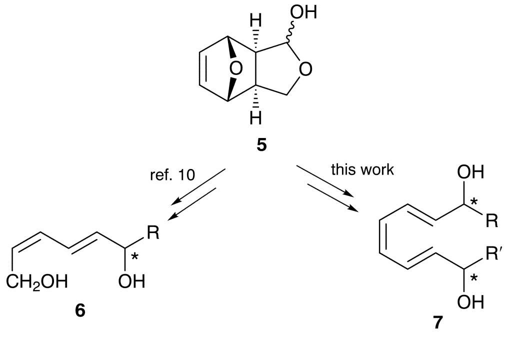
A versatile and stereoselective synthesis of dihydroxy-(*E*,*Z*,*E*)-conjugated trienes, involving a palladium(II)-catalyzed two-fold [3,3] rearrangement, is reported.

The structure of a number of metabolites of arachidonic acid arising from the lipoxygenase pathways are characterized by the presence of conjugated dienic, trienic or even tetraenic systems of well defined geometry.[1] We had previously described,[10] starting from lactol **5**, a highly diastereoselective synthesis of (*E*,*Z*)-conjugated dienols **6** with a hydroxy group of *R* or *S* configuration next to the *E* double bond, a common moiety of all the HETEs.

We wish to report here an extension of this methodology to the stereoselective synthesis of dihydroxy-(*E*,*Z*,*E*)-conjugated trienes **7**, a system found in a variety of arachidonic acid metabolites such as di-HETEs. The feasibility of our strategy has been checked for **7** ($R = R' = C_5H_{11}$), starting from racemic lactol (±)-**5** (Scheme 1).

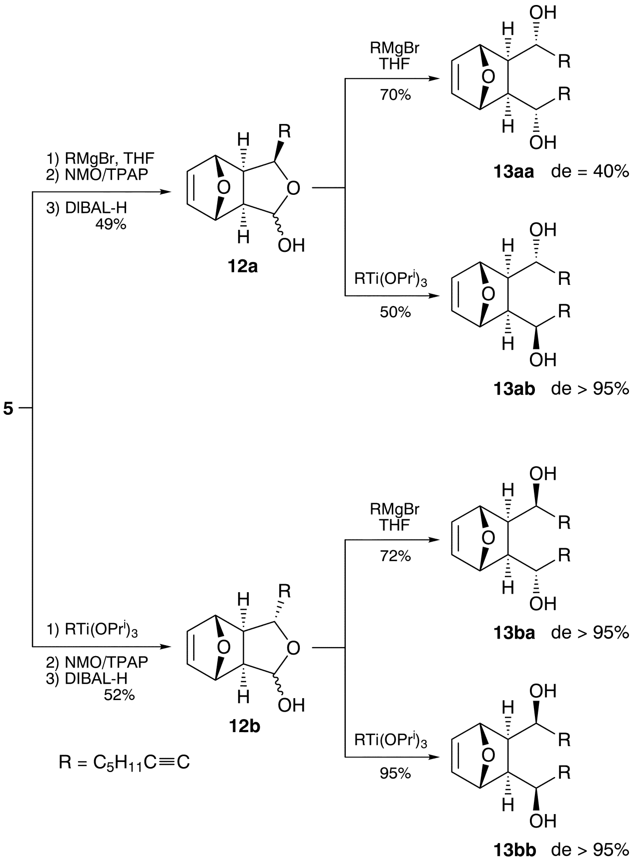


Scheme 1

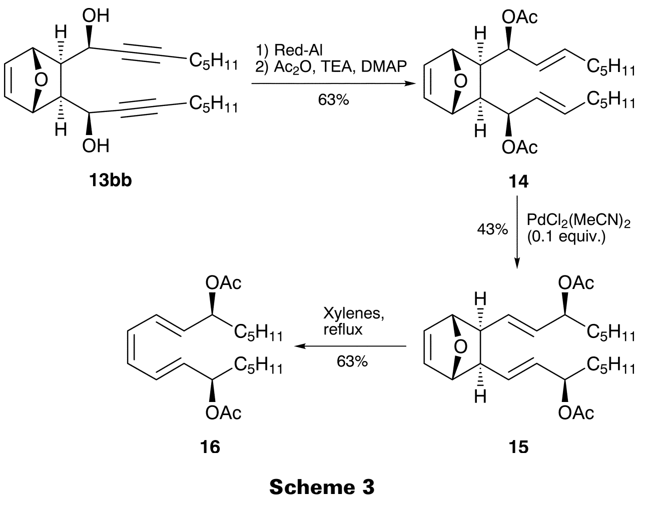
The first problem to solve was the control of the relative configurations of the two stereogenic carbons bearing the hydroxy groups. We had shown[10] that the addition of metal acetylides to the *Si* or *Re* face of the C=O bond of the open form of lactol **5** can be controlled by the nature of the metal (magnesium or titanium) to afford either one or the other diastereomeric diol with high selectivity (de = 76–82%). Oxidation of these diols with NMO/TPAP[14] followed by reduction with diisobutyl aluminum hydride gives access to the lactols **12a** and **12b** (Scheme 2).

The addition of organometallic reagents derived from hept-1-yne to these lactols proved to be highly stereoselective and it is relatively easy to obtain, starting from the same lactol **5**, one of the diastereomers of the diol **13**. In our case, owing to the symmetry of the molecule, only three diastereomers have been obtained since **13ab** is equivalent to **13ba**.

The diol **13bb** has been chosen arbitrarily to carry on with the synthetic scheme. After selective *trans*-reduction of the two triple bonds of **13bb** (Scheme 3), followed by acetylation of the hydroxy groups, the diacetate **14** was treated with a catalytic amount of bis(acetonitrile)palladium(II) chloride in THF at room temperature.[12] In these conditions a double allylic rearrangement occurred to give the single diacetate **15**. The success of this twofold [3,3]-rearrangement



Scheme 2



Scheme 3

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is probably due here to the relief of steric congestion around the two acetoxy groups of the rigid bicyclic system. Heated at 130 °C in xylene, **15** extruded furan to give the (*E*,*Z*,*E*)-triene **16** stereochemically pure.

In conclusion, a stereoselective and versatile synthesis of dihydroxytrienes of type **7** has been established, which could be applied to the preparation of enantiomerically pure diastereomers, starting from the easily available[17] homochiral lactols **5**.

Techniques used: ^{1}H and ^{13}C NMR, IR, mass spectrometry

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