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Remote Asymmetric Induction in Palladium-Catalyzed Oxidative Cyclization of 2,6-Heptadienoates

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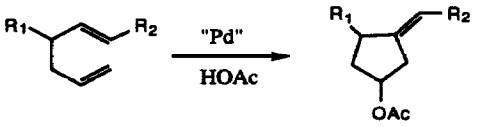
Abstract: 1,8-Asymmetric induction (35% de) was observed in oxidative palladium-catalyzed cyclization of (1*R*,2*S*,3*R*)-2-neopentoxy-3-bornanyl 2,6-heptadienoate.

Palladium-catalyzed oxidative cyclization of 1,5-dienes[1] (eq 1) constitutes an attractive method for the synthesis of cyclopentane derivatives.[2] In certain cases, the reaction proceeds with high diastereoselectivity.[1] To widen the scope of the reaction, it was of interest to develop methods that would allow control of the absolute stereochemistry as well. This was achieved by replacing acetic acid as nucleophile with chiral acids,[3] which under proper reaction conditions (in the presence of molecular sieves) resulted in an enantioselection of up to 76%.[4]



eq 1

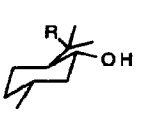
Another possibility in achieving chiral induction would be to attach a chiral auxiliary to the reacting diene. Conjugated esters of chiral alcohols derived from camphor or menthol, for example, show high facial selectivity in reactions such as Diels Alder additions,[5] conjugate additions,[6] enolate alkylations,[5,7] Paterno-Büchi photoadditions,[5] bishydroxylations[5] and nickel-catalyzed [3+2] cycloadditions.[8] This selectivity is believed to originate in the fact that in the preferred conformation, one face of the olefin is blocked and consequently only one diastereoface remains exposed to the reagent.

In the palladium-catalyzed cyclization, attack of the nucleophile (acetate ion) takes place at the least substituted olefinic bond. When esters of 2,6-heptadienoic acid derived from chiral alcohols (R_1 = H and R_2 = COOR* in the 1,5-diene) are subjected to the palladium-catalyzed oxidative cyclization, the new stereogenic center will thus be situated seven bonds away from the existing one. However, since the conformational freedom of the diene system is restricted due to the intermediate formation of a Pd(II) diene complex,[9] it occurred to us that the facial selectivity might also be transferred to the remote olefinic bond of the 2,6-heptadienoate system.

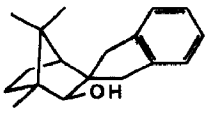
Esters of 2,6-heptadienoic acid (R_1 = H and R_2 = COOR* in the 1,5-diene) were thus prepared, via reaction of triethylphosphonoacetate[10] with the appropriate chiral alcohol,[11] followed by condensation with 4-pentenal, in turn obtained by Swern oxidation of the corresponding alcohol,[12] and then subjected to cyclization.

Use of (-)-menthol (**1a**) and (-)-8-phenylmenthol (**1b**) as chiral alcohols was first attemped. The expected cyclic products were formed, but no asymmetric induction was observed by NMR spectroscopy or by HPLC. We therefore turned to esters derived from camphor. The heptadienoic ester derived from spiro compound **2**[7] was subjected to the cyclization reaction.[13] According to HPLC, a mixture of two compounds was obtained, assumed by NMR spectroscopy to be the expected cyclic acetates. The ratio of the isomers was determined from NMR and HPLC to be 1.27:1, corresponding to a de of ca 12%. The structure of the products was verified by independent synthesis starting from the carboxylic acid obtained by palladium-catalyzed cyclization of 2,6-heptadienoic acid[14] and alcohol **2**, which afforded a 1:1 mixture of the same isomers.

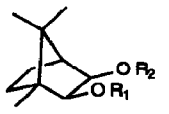
Heptadienoic esters prepared from the alcohols **3** and **4** also afforded the expected cyclized products (identical by NMR spectroscopy and HPLC to independently prepared samples). In the cyclization of dienes derived from naphthyl alcohols **3a** and **4a** only low (ca 10%) diastereoselectivity was observed. However, the esters obtained from alcohols **3b** and **4b** both gave the two products expected in each case in unequal amounts, corresponding to 25% de in both cases. At lower temperature, -20 °C, reaction of the ester prepared from **4b** resulted in a de of 35%.[15]



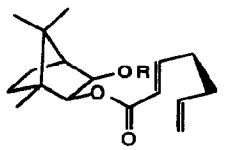
1a R = H
1b R = Ph



2



3a R_1 = H, R_2 = naphtyl
3b R_1 = H, R_2 = neopentyl
4a R_1 = naphtyl, R_2 = H
4b R_1 = neopentyl, R_2 = H



The chiral induction observed in the present reactions is lower than that usually observed in cases when the olefinic bond conjugated to the ester is functionalized. However, what is interesting here is that the newly formed stereogenic center is situated *seven* bonds instead of four bonds away from the center responsible for chiral induction. The only case that we are aware of where this type of long-range chiral induction has been achieved in a similar system is the intramolecular conjugate addition of chiral β-ketoesters.[16]

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13. Experimental: 0.25 mmol of the diene was stirred at room temperature with 0.1 eq of $Pd(OAc)_2$, 0.25 eq of *p*-benzoquinone and 1 eq of MnO_2 in 3 ml of acetic acid for 4 days.
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