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Chirality Transfer in the Palladium(0)-Catalyzed Cyclization of 3-Oxo-8,9-dihydroxytetradeca-1,6-diene Derivatives into 2-Methylenecyclopentanones

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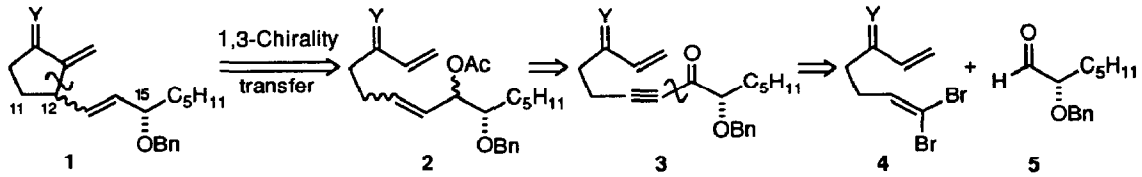
Abstract: Pd(0)-catalyzed cyclizations of four diastereomeric 3-oxo-8,9-dihydroxytetradeca-1,6-diene derivatives were carried out to give 2-methylenecyclopentanones with stereospecific 1,3-chirality transfer in up to 95% overall inversion of stereochemistry, one of which contains a correct ω-side chain to be the Stork's intermediate for prostaglandins.

An intramolecular allylation of a soft carbonucleophile via the π-allylpalladium readily forms a 6-membered ring,[1] where the 1,3-chirality transfer can be realized from the chiral allylic moiety to the newly created carbon-carbon linkage with almost complete overall retention of configuration.[2] However, attempted cyclization for a 5-membered ring with a β-keto ester is known to undergo kinetically favored *O*-allylation rather than *C*-allylation.[1b,3] Aiming at the construction of 5-membered carbocycles, we have reported a novel intramolecular olefin insertion into the π-allylpalladium intermediates followed by carbonylation starting from 2,7-octadienyl acetate systems.[4,5] The process can end up with β-hydrogen elimination to form 2-vinyl-methylene-cyclopentanes, being referred to as a palladium-ene reaction.[5]

In our continuing study on the synthetic routes to prostaglandins (PGs), we describe herein a new approach to the Stork's intermediate[6] using the Pd(0)-catalyzed olefin insertion strategy (**2** → **1**) as depicted in a retrosynthetic Scheme 1. If this approach serves to control the 1,3-chirality transfer via a π-allylpalladium, one may construct the methylenecyclopentanone skeleton, in one step, by a unique C-C bond formation and also the correct ω-side chain for the 11-deoxy-Stork's intermediate. Since the intramolecular olefin insertion would take place from the palladium coordination sphere of the π-allylpalladium moiety,[7] we have examined the stereochemical integrity during the Pd-catalyzed cyclization using four possible diastereomeric 3-oxo-8,9-dihydroxytetradeca-1,6-diene derivatives **2**.

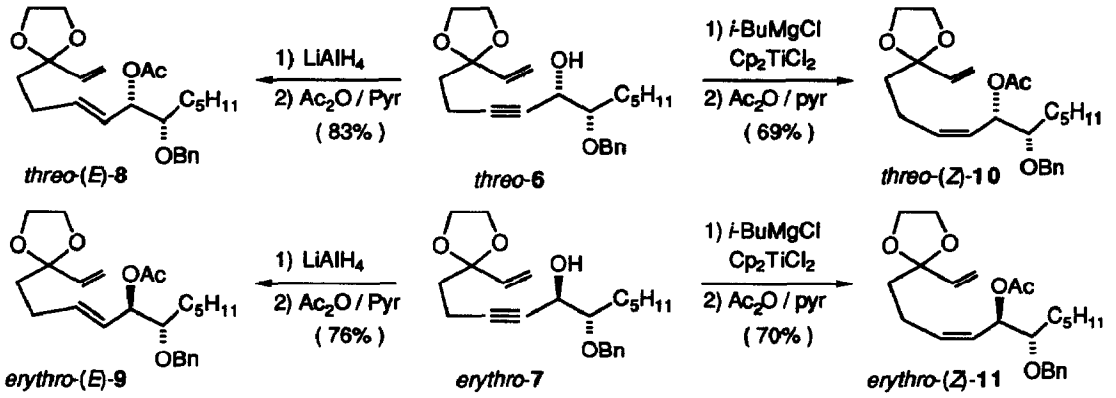


a : Y = $O(CH_2)_2O$, **b** : Y = O ; Bn = Benzyl

Scheme 1

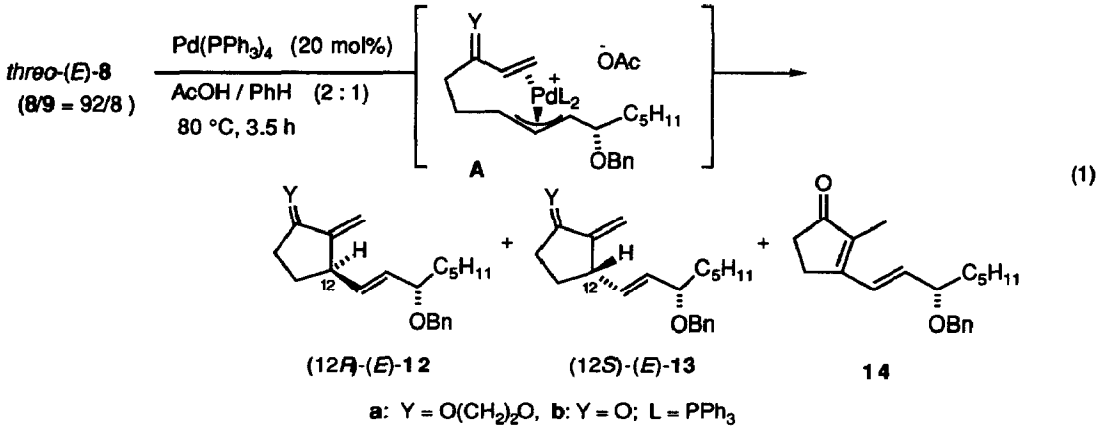
One component **4a** was prepared starting from 2,3-dihydrofuran.[8] Another one, (*S*)-2-benzyloxyheptanal (**5**),[9] was derived from optically pure epichlorohydrin in seven steps: Then, **4a** was treated with BuLi (2 equiv) in THF at -78 °C and **5** was added to the mixture to give a diastereomeric mixture (ca 1 : 1) of alcohol **6** and **7** (*vide infra*) (91% yield), which was in turn converted by the Swern oxidation to the corresponding acetylenic ketone **3a** in quantitative yield. Stereoselective reduction of **3a** using either K-selectride or zinc borohydride[10]

gave *threo*-**6** (91%) and *erythro*-**7** (83%), respectively. Furthermore, trans-selective $LiAlH_4$ reduction of the resulting threo (**6**/**7** = 90/10) or erythro (**6**/**7** = 9/91) acetylenic alcohol gave, after acetylation, *threo*-(*E*)-**8** (**8**/**9** = 92/8) and *erythro*-(*E*)-**9** (**8**/**9**= 0/100), respectively, in satisfactory overall yields as depicted in Scheme 2. In the similar manner, cis-selective hydromagnesiation[11] of **6** and **7** [*i*-BuMgCl (2 equiv) and Cp_2TiCl_2 (30 mol%)] followed by acetylation afforded *threo*-(*Z*)-**10** and *erythro*-(*Z*)-**11**, respectively (Scheme 2).



Scheme 2

Pd(0)-catalyzed cyclizations of the allylic acetates **8**-**11** were carried out in the presence of $Pd(PPh_3)_4$ (20 mol%) in AcOH-PhH (2 : 1) at 80 °C for 3.5 h.[12] Thus, **8** (**8**/**9** = 92/8) was smoothly cyclized via the π-allylpalladium **A** to form diastereomeric mixtures of (12*R*)-(*E*)-**12a**, (12*S*)-(*E*)-**13a** (36%)[13] and **12b**, **13b** (27%)[13] along with the endo enone **14** (14%) and small amounts of Z diastereomers corresponding to **12b**, **13b** (2%) (eq. 1). The reaction products, without isolation, were deacetalized and HPLC analysis of the mixture indicated that the ratio of **12b** and **13b** was 87 : 13. The absolute stereochemistry at C_{12} (PG numbering) of the



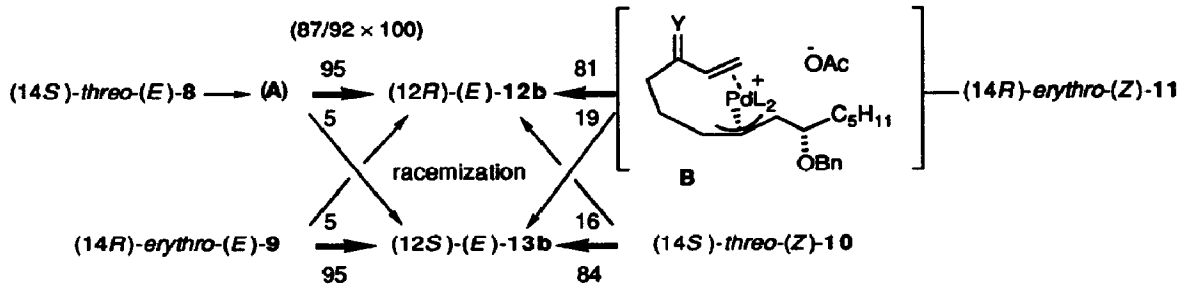
(1)

a: Y = $O(CH_2)_2O$, **b**: Y = O; L = PPh_3

major diastereomer **12b** was determined to be R on the basis of NMR and CD spectra of the corresponding diastereomeric α- and β-allylic alcohols,[14] which were obtained by DIBAL reduction of the purified **12b** and separated by HPLC. Prolonged reaction (10 h) for the cyclization of **8** resulted in giving **12b**, **13b** (46%, the ratio 89/11) and **14** (36%). From **9**, in 3.5 h heating, were obtained mixtures of **12a**, **13a** (33%), and **12b**, **13b** (17%), **14** (8%), and again small amounts (2%) of Z diastereomers. HPLC analysis of the deacetalized mixture of **12b**, **13b** revealed that the major diastereomer was the epimer at C_{12} and thus the ratio of **12b** and

13b was 5 : 95. On the other hand, the Pd(0)-catalyzed cyclizations of **10** as well as **11** (both diastereomerically pure), under the same reaction conditions as described above but for 5 h of heating, afforded **13b** in 56% (**12**/**13** = 16/84) and **12b** in 64% (**12**/**13** = 81/19) yield, respectively.

Thus, all results obtained with respect to the stereochemical outcome are compiled in Scheme 3. We can



Scheme 3

delineate several stereochemical features of the intramolecular olefin insertion of four diastereomeric substrates **8**-**11**: (i) The acetals (12*R*)-(*E*)-**12a** and (12*S*)-(*E*)-**13a** (see eq. 1) must be immediate products,[12] and deacetalized **12b** and **13b** as well as isomerized **14** are secondary products, Z diastereomers being by far minor ones. (ii) The stereochemical integrity observed in the cyclizations, via π-allylpalladium, of two diastereomers **8** and **9** was 95% on the average with overall inversion of configuration, whereas the cyclizations of other two diastereomers **10** and **11** exhibited lower level of 1,3-chirality transfer with *ca.* 82% stereospecificity. (iii) The fact that all four substrates **8**-**11** gave either **12b** or **13b** indicates that the olefin insertion always occurs from the palladium site and that an extensive anti → syn isomerization of π-allylpalladium **B** is involved prior to cyclization. (iv) The reason why a significant loss of stereospecificity was observed in the cyclizations of **10** and **11** would be the racemization at the local structure of 1,3-disubstituted π-allylpalladium **B** by an S_N2-type attack of Pd(0) catalyst,[2b,15] while this is also the case but less significant for **8** and **9**.

In conclusion, (14*S*)-*threo*-(*E*)-**8**, one of the four diastereomeric 3-oxo-8,9-dihydroxytetradeca-1,6-diene derivatives **2a**, can be cyclized to form the Stork's intermediate for PG with a 95% stereospecific 1,3-chirality transfer.

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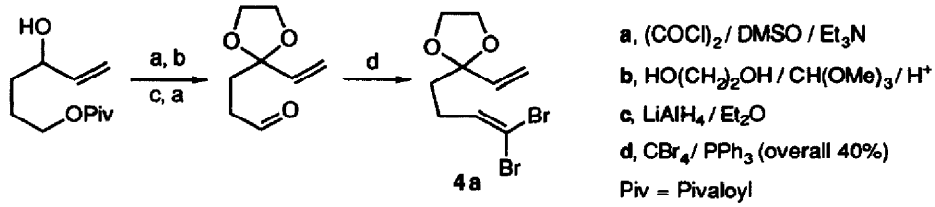
7. Oppolzer, W.; Birkinshaw, T.N.; Bernardinelli, G. *Tetrahedron Lett.* **1990**, *31*, 6995. In the Pd-catalyzed pyrrolidine formation from 6-aza-4-acetoxy-2,8-nonadienes an efficient chirality transfer has been observed via intramolecular olefin insertion.
8. Scheme 3 for the preparation of **4a** given:



Scheme 4

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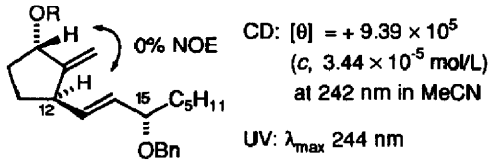
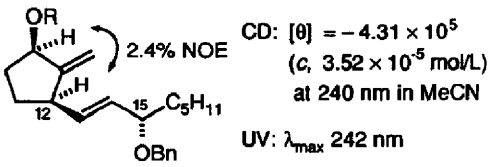
11. Sato, F. *J. Organomet. Chem.* **1985**, *285*, 53 and references therein.
12. The reaction conditions having been determined on the basis of preliminary experiments using diasteromeric mixture of racemic **8** and **9** to be cyclized (68% yield), since acetal protection in **8** (and **9**) is indispensable for the present reaction: Terakado, M. presented at the 61st General Meeting of the Chem. Soc. Jpn. (1991, Yokohama), Abstr. 1D212.
13. Diastereomer ratios (dr) were determined by both ^1H NMR and HPLC of diastereomeric mixtures, each component being separated by HPLC and identified by spectral data. NMR data of major (*E*)-**12b** given: ^1H NMR (270 MHz, $CDCl_3$, TMS) 0.88 (t, J = 6.8 Hz, 3H), 1.2-1.6 (m, 6H), 1.6-1.8 (m, 2H), 2.2-2.5 (m, 4H), 3.3-3.5 (m, 1H), 3.76 (q, J = 6.6 Hz, 1H), 4.38 (d, J = 12.1 Hz, 1H), 4.58 (d, J = 12.1 Hz, 1H), 5.22 (dd, J = 1.0, 2.6 Hz, 1H), 5.4-5.6 (m, 2H), 6.08 (dd, J = 1.0, 3.1 Hz, 1H), and 7.3-7.4 (m, 5H). $^{13}C\{^1H\}$ NMR (67.8 MHz) 14.0, 22.6, 25.2, 27.4, 31.7, 35.7, 37.2, 44.8, 70.1, 79.7, 118.2, 127.4, 127.7, 128.3, 133.4, 133.8, 138.8, 147.6, and 206.3.
14. DIBAL reduction of major **12b** gave an α-alcohol, (*E*)-**15**-α (R = H), and β-alcohol, (*E*)-**16**-β (R = H), in a ratio 1.6 : 1.0 (by NMR). The relative stereochemistry was determined unequivocally by an NOE measurement shown below and the absolute stereochemistry was decided as indicated on the basis of signs of CD spectra of respective *p*-bromobenzoate (R = COC_6H_4Br-*p*) of the cyclic allylic alcohols.[6c]



(12*R*,15*S*)-(*E*)-**15**-α



(12*R*15*S*)-(*E*)-**16**-β

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