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PALLADIUM-CATALYZED CHIRALITY TRANSFER OF 1,3-DIENE MONOEPOXIDES AND ITS APPLICATION TO THE SYNTHESIS OF STEROID SIDE CHAINS

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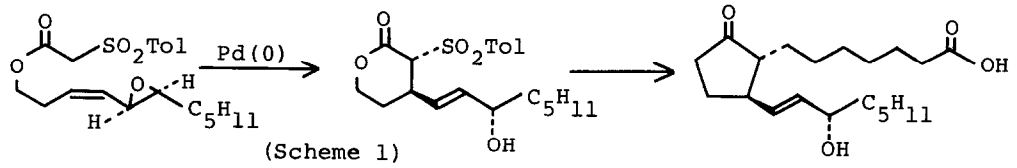
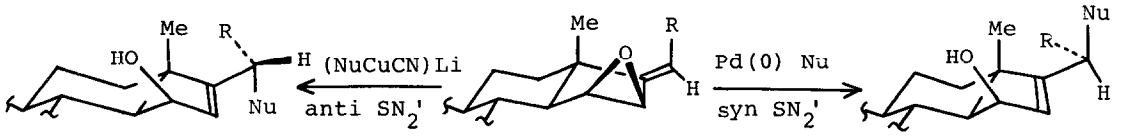
Summary: The palladium-catalyzed 1,4-addition of nucleophiles to 15β,16β-epoxy-E-$\Delta^{17(20)}$-isoheptylidene steroid **8** and 15β,16β-epoxy-E-$\Delta^{17(20)}$-ethylidene steroid **13** has been studied as a good method for regio- and stereoselective introduction of steroid side chains.

The regio- and stereoselective C-C bond formation in acyclic and cyclic systems is an important operation in organic syntheses.[1] In this connection palladium-catalyzed allylation[2] and coupling reaction of organocuprate with allylic compounds[3] offer some solutions. Particularly palladium-catalyzed regioselective reaction of 1,3-diene monoepoxides with nucleophiles is a promising reaction.[4] Recently we have reported the regio- and stereoselective palladium-catalyzed syn S_cN'[5] cyclization of 1,3-diene monoepoxide and its application to the synthesis of 11-deoxy PGE_1 (Scheme 1).[6]



(Scheme 1)

Coupling of alkyl cyanocuprate with the steroidal 1,3-diene monoepoxide **1** has recently been reported by Marino.[7] This coupling reaction proceeds with anti attack and competitive 1,2- and 1,4-additions at the allylic system (**1** → **2**). Now we wish to report that the palladium-catalyzed allylation of nucleophiles with the 1,3-diene monoepoxide **1** gives only 1,4-addition product with syn relationship of the entering and departing group (**1** → **3**). This palladium-catalyzed syn SN_2' reaction would be valuable for the transfer of C-O chirality to that of a carbon atom of the newly formed C-C bond. We examined this

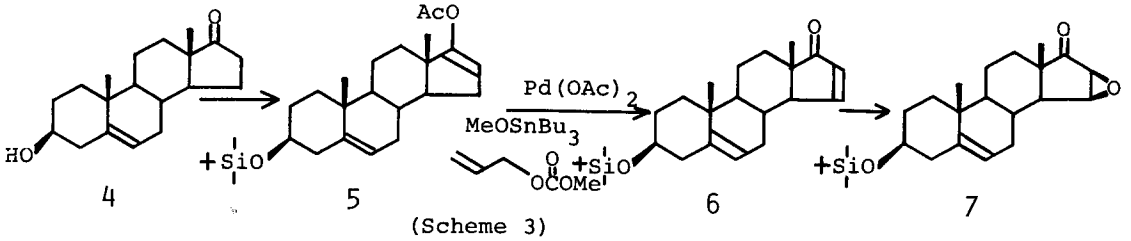


2 1 3

(Scheme 2)

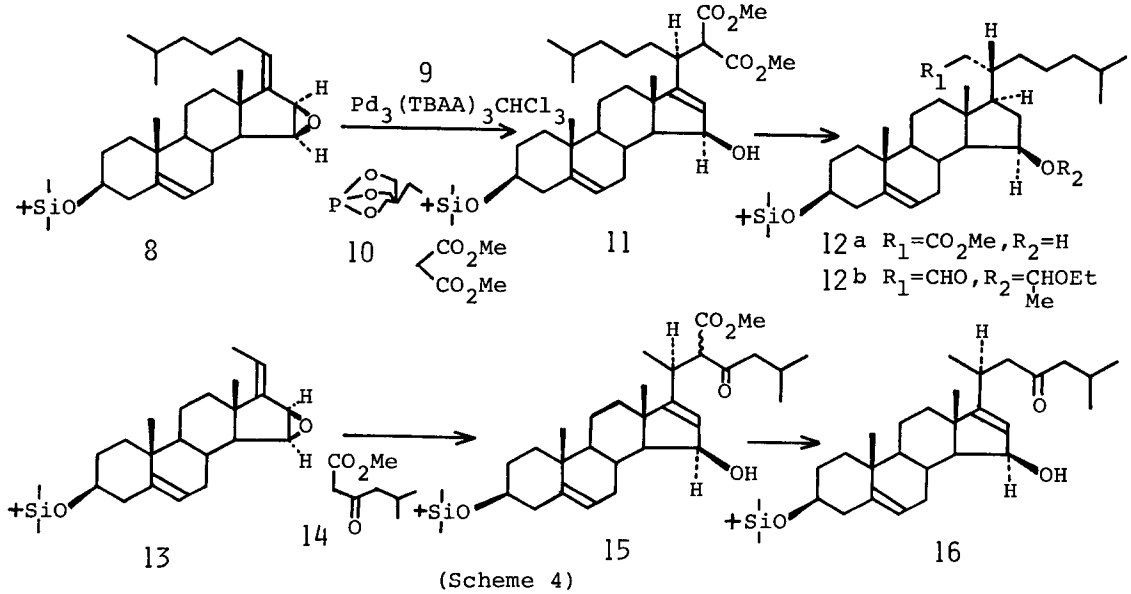
concept within the context of the stereoselective construction of the C(20R) and C(20S) configurations[8] in steroid side chains. In addition, this reaction is useful for the introduction of 15-hydroxy group, which is found in naturally occurring oogoniol.[9]

Although the 15β,16β-epoxy-17-ketone **7** has been synthesized[7,10] from dehydroepiandrosterone (**4**) in eight steps, we prepared the same ketone **7** from **4** in four steps as outlined in the Scheme 3 applying our method of palladium-catalyzed enone formation from enol acetate.[11] Protection of the alcohol **4** (tert-$BuMe_2SiCl$/imidazole/DMF; 95% yield) and transacetylation with isopropenyl acetate gave the enol acetate **5** in 80% yield. The palladium-catalyzed enone formation [**5** (10 mmol), allyl methyl carbonate (20 mmol), $Pd(OAc)_2$ (0.5 mmol) and tributyltin methoxide (3.5 mmol) in dry CH_3CN (120 mL); reflux 2h] gave the enone **6** in 82% yield after column chromatography. The stereoselective epoxidation[10b] of the enone **6** and subsequent Wittig reactions of the resultant epoxy ketone **7** with ethyl- and isoheptyltriphenylphosphonium bromides afforded the desired epoxides **8** and **13**.[7]



(Scheme 3)

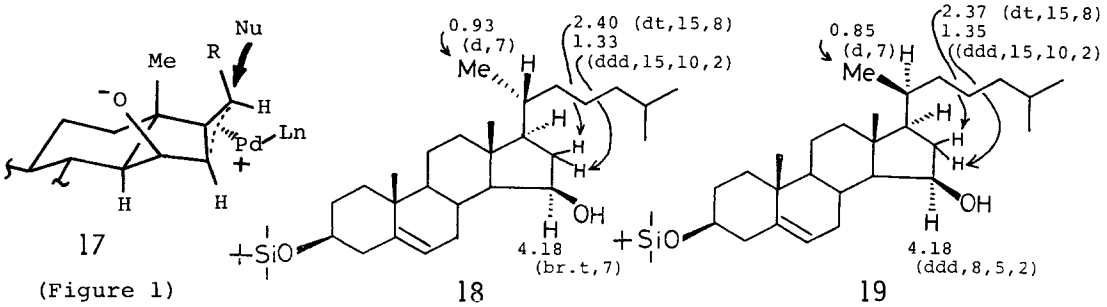
Reactions of the alkylidene epoxides **8** and **13** with nucleophiles were carried out in the following way (Scheme 4). A solution of palladium(0)



(Scheme 4)

complex **9** (0.016 mmol) and phosphite ligand **10** (0.139 mmol) in dry THF (6 mL) was stirred for 30 min at room temperature under argon. After color of the solution changed from brown to yellow, a solution of the epoxide **8** (0.88 mmol) and dimethyl malonate (3.0 mmol) in dry THF (6 mL) was added in one portion. The reaction mixture was stirred for 2 h at room temperature and the 1,4-addition product **11** was isolated in 80% yield after column chromatography. No regio(1,2-addition)- and stereoisomer was detected by careful examination of ^{13}C NMR spectrum and HPLC. In a similar manner, the epoxide **13** was allowed to react with β-ketoester **14** to give the 1,4-addition product **15** in 85.7% yield as a mixture of stereoisomers due to the methoxycarbonyl group. After demethoxycarbonylaton of **15** (NaI/HMPA/H_2O at 180 °C; 75% yield) to form **16**, the regio- and stereoselectivity of the palladium-catalyzed reaction was examined and no isomer of **16** was detected by ^{13}C NMR spectrum and HPLC. Then the absolute stereochemistry at C(20) of the 1,4-addition products **11** and **15** was determined by conversion to the 15β-hydroxycholesterol **18** and 15β-hydroxyisocholesterol **19**, respectively. These results and mechanistic consideration based on previous work[6,12] indicate that the initial attack of palladium(0) took place from the opposite face of epoxide to form π-allylpalladium complex **17** and the following attack of nucleophile proceeded, without isomerization of syn syn complex **17**, from the opposite face of π-allylpalladium as shown in figure 1.

Transfromation of the diester **11** into 15β-hydroxycholesterol **18** was carried out in the following way. Demethoxycarbonylation of **11** (NaI/HMPA/H_2O at 180 °C) and selective hydrogenation[7] of the Δ^{16}-double bond over Pt_2O gave the alcohol **12a**. Protection of the alcohol **12a** with ethyl vinyl ether and conversion of the ester group to aldehyde in two steps ($^{i}Bu_2AlH$ in THF, Collins oxidation in CH_2Cl_2) gave **12b** in 85% overall yield. Decarbonylation[13] of the aldehyde **12b** with $Rh(PPh)_3Cl$ in refluxing benzene, removal of both protecting groups (PPTS/MeOH at 0 °C) and the selective silylation of 3-hydroxy group (tert-$BuMe_2SiCl$/imidazole) gave the known alcohol **18**.[7] The conversion of the ketone **16** into 15β-hydroxyisocholesterol **19** was carried out in the following way. Wolff-Kishner reduction of the ketone **16**, selective hydrogenation of Δ^{16}-olefin and silylation of 3-hydroxy group gave the alcohol **19**.[7] Comparison of



17 18 19

(Figure 1)

the NMR spectra (360-MHz) of the alcohols **18** and **19** nicely distinguishes the two isomers in the C(20)-methyl region (see the diagram).

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