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A POSSIBLE WAY FOR THE INTRODUCTION OF α- AND β-FORMYL-ETHYL-SUBSTITUENTS INTO THE STEROID-SKELETON VIA COUPLING AND CARBONYLATION REACTIONS

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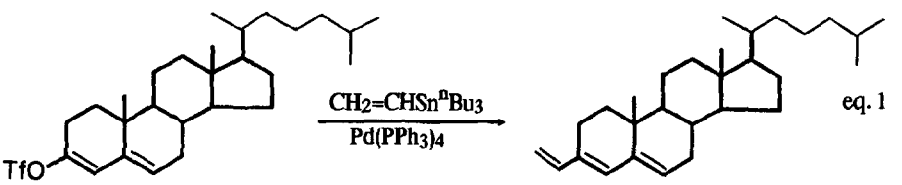
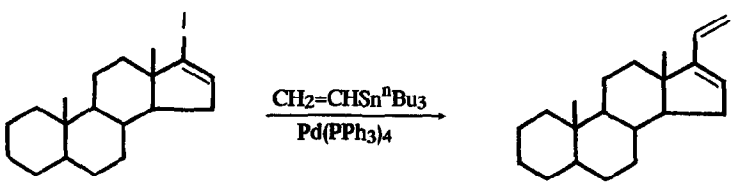
Abstract: Cholesta-3,5-dien-3-yl triflate and androsta-16-en-17-yl iodide were vinylated with palladium and the olefins hydroformylated in the presence of rhodium and platinum catalysts.

Till now there are very few examples for the functionalization of steroids via homogeneous carbonylation[1] and coupling reactions. Lately enol triflates derived from keto-steroids have been used for the β-vinylation of vinyl acetate in the presence of palladium catalysts [2]. An additional possibility for the vinylation is the cross-coupling reaction of enol-triflates and vinyl-stannanes[3]. Indeed, to our knowledge, no example for the Stille-coupling using steroids has been reported so far.

As described for different type of triflates even the vinylation of cholesta-3,5-diene-3-yl triflate **1** takes place almost quantitavely using vinyltributyltin[4] and $Pd(PPh_3)_4$ as catalytic precursor (eq. 1). We have found that not only the triflates but also the "iodo-vinyl" derivative reacts very efficiently under the same conditions (eq. 2). The reaction is completely chemoselective, no additional products have been observed even in traces. The isolated yields are 65% and 59%, respectively.



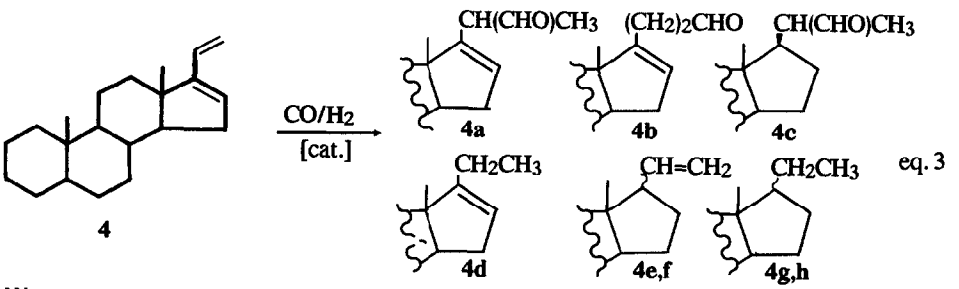
1 **2** eq. 1



3 **4** eq. 2

In a typical procedure a mixture of androsta-16-ene-17-yl iodide **3** (768mg., 2mmol) $Pd(PPh_3)_4$ (46mg., 0.04mmol) vinyltributyltin (700mg., 2.2mmol) and approximately 5mg of t-butylcatechol in toluene were reacted under argon at 110°C for 4 hours. After removal of the solvent in vacuo the residue was dissolved in petroleum ether and chromatographed on silica in the same solvent. The crude product was dissolved in diethyl ether and steroid crystallised by adding methanol. After filtration the product **4** [5] was washed with methanol several times.

Under hydroformylation conditions further functionalisation of the conjugated diene **4** was effected (eq 3). The most active catalyst proved to be $[Rh(nbd)Cl]_2$ plus PPh_3 in relation both to the corresponding DIOP-containing rhodium catalyst and to $PtCl(SnCl_3)DPPE$. For the first-named case, conversion is close to 100% in 3 hours at 100°C using 80bar pressure ($CO / H_2 = 1:1$) but the other catalysts give respectively 65% and 50% completion under identical conditions. Whilst the chiral aldehyde **4a** was formed in ca. 75% regioselectivity with $Rh\text{-}PPh_3$ or Pt, this is only a minor product with the DIOP-derived catalyst, where the linear aldehyde **4b** is preferred. In addition[6], compounds **4d** - **4f** were by-products to the Pt-catalysed reaction, and some hydrogenation together with production of **4c** was observed in the Rh-catalysed reaction[7]. Efforts are continuing to develop these observations into a hydroformylation-based asymmetric synthesis of the steroidal side-chain.



eq. 3

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4. It was prepared as described in E.M.Smolin, Tetrahedron Lett., **1961**, *4*, 143

5. Spectroscopic data for **4**: ^1H NMR (δ,$CDCl_3$): 6.30 (dd,J=18Hz,12Hz,1H,=$C^{20}H$); 5.69 (t,J=2.5Hz,1H, =$C^{16}H$); 5.32 (d,J=18Hz,1H,=$C^{21}H_a$); 4.95 (d,J=12Hz,1H,=$C^{21}H_b$); 2.1 (m,1H,$C^{15}H_{eq}$); 1.86 (m,1H, $C^{15}H_{ax}$); 2.05 (m,1H,$C^{14}H$); 0.8-1.70 (m,19H, **ring protons**); 0.92 (s,3H,$C^{18}H_3$) 0.82 (s,3H,$C^{19}H_3$); ^{13}CNMR (δ,$CDCl_3$): 152.4; 131.5; 128.4; 111.6; 56.4; 54.1; 46.1; 45.3; 37.6; 35.5; 34.4; 33.0; 28.0; 25.8; 21.1; 19.8; 15.0; 11.2; MS (m/z/rel.int.) :284/31% (M^+); 269/100%; 120/64%; 105/54%; 91/42.5%;

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7. The mixture of the formyl-products were analyzed by GC-MS and ^1H NMR.