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STEREOSPECIFIC 6β-FUNCTIONALISATION OF 3-OXO-4-ENE STEROIDS VIA π-ALLYLPALLADIUM COMPLEXES

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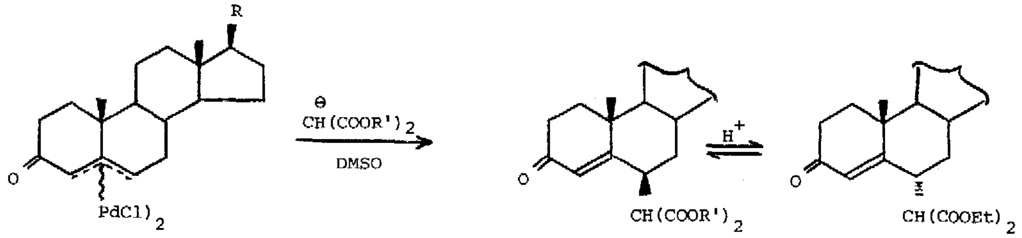
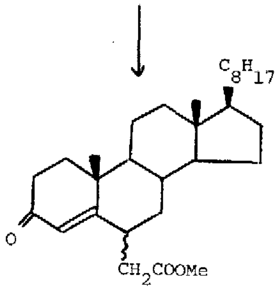
We wish to report an efficient stereospecific two-step 6-functionalisation of 3-oxo-4-ene steroids *via* their π-allylpalladium complexes. Thus, reaction of cholest-4-en-3-one, or testosterone, with palladium chloride in refluxing tetrahydrofuran containing an excess of sodium chloride gave the complexes (1a) and (1b) in 71% and 88% yield, respectively. The physical constants of the complexes were in general agreement with those reported previously.[1] The complexes were tentatively assigned the α-4-6η stereochemistry from general considerations, and by analogy with the preferred formation of α-isomers from reactions of cholest-4- and -5-enes with palladium chloride.[2] Solutions of the palladium complexes (1a) and (1b) in dry dimethylsulphoxide were allowed to react at room temperature with the anions of dimethyl and diethyl malonate, generated using sodium hydride in dry dimethylsulphoxide, to give up to 90% yield of the esters (2a, b, c, or d). However when ethanol or methanol were present in the



(1a) R = C_8H_{17}
(1b) R = OH

(2a) R = C_8H_{17}, R' = Me
(2b) R = C_8H_{17}, R' = Et
(2c) R = OH, R' = Me
(2d) R = OH, R' = Et

(3) R = C_8H_{17}



(4)$_2$

reaction medium the yields of the esters (2) were low and significant amounts of the 6-unsubstituted 4,6-dien-3-ones were also formed. Harrison et al.[3] reported exclusive dienone formation in the reaction of malonate ion with a 3-oxo-4-6η-steroid palladium complex. Our alkylation reaction proceeded both regio- and stereospecifically to give the 6β-substituted compounds. The p.m.r. spectrum of diethyl (cholest-4-en-3-one)-6β-ylmalonate showed the 4-proton as a singlet, and the 6α-proton at δ3.21 as a doublet of doublets with $^3J_{6\alpha,6'}$ 12 Hz, and $^3J_{6\alpha,7}$ 4.5 Hz. The lack of significant allylic coupling and the lack of a large axial-axial coupling for the 6 proton are consistent with 6β-pseudo-axial stereochemistry for the substituent. This was confirmed by the ready acid-catalysed isomerisation of (2b) to the corresponding 6α-isomer (3) when (2b) was heated with p-toluenesulphonic acid in benzene. The 6α-isomer showed the 4-vinylic proton at δ5.51 as a doublet with $^4J_{4,6\beta}$ 2.0 Hz, and the 6β-H as a very broad multiplet centered at δ3.2. The other esters (2, a, c, and d) were also assigned the 6β-stereochemistry on the basis of their n.m.r. spectra. The p.m.r. spectra of the crude alkylation products showed no evidence for the presence of the α-isomer. If our assignment of α-4-6η stereochemistry to the palladium complex is correct the displacement reaction proceeds with complete inversion. A similar inversion of stereochemistry has been reported for the alkylation of other π-allylpalladium system.[4]

Decarbomethyoxylation of (2a) with lithium iodide in dimethylformamide gave a 6:1 mixture of the 6α- and 6β-isomers of methyl (cholest-4-en-3-one)-6-ylacetate (4) in 70% yield. The esters (4) were identified by direct comparison with authentic specimens prepared by an unambiguous route.[5] The conditions for the decarbomethoxylation reaction have not yet been optimised, but our route gives a high overall yield (at least 46%) of the 6-carboxymethyl steroids. These compounds have potential use in radioimmunoassay but have previously been available only by multiple-step syntheses with low overall yields.[5,6]

All new compounds gave correct microanalyses.

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