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Functionalization of the estrone skeleton via homogeneous coupling and hydroformylation reactions

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Abstract

The estrone triflate (3-trifluoromethylsulfonate-estra-1,3,5(10)-triene-17-one) was vinylated by use of vinyltributyltin in the presence of palladium catalysts. The rhodium- and platinum-catalysed hydroformylation of the vinylated aromatic steroid gave the pure epimer 3-(2'-formylethyl)-estra-1,3,5(10)-triene-17-one.

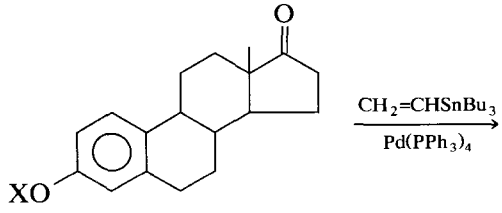
1. Introduction

Although both the cross-coupling reaction of enol triflates with vinyl-stannanes [1–8] and the hydroformylation of functionalized olefins [9–11] seem to be of practical importance in synthesis, there are very few examples of the consecutive use of these reactions for the further functionalization of biologically important skeletons [12,13]. The synthesis of important α-arylpropionic acids with anti-inflammatory effects (Ibuprofen, Naproxen, Suprofen) have been the focus of a major research effort in recent years [14–17]. Stille reported the preparation of these compounds by use of asymmetric hydroformylation of the vinyl aromatics as a "key-reaction" [13]. We are aware of no previous studies concerning the combination of the cross-coupling and hydroformylation reactions involving styrenic estrogens, where the aryl-substituent in the resulting α-substituted propanal is the estrene moiety itself. Little attention has been paid to the carbonylation of steroids either [12,18–20].

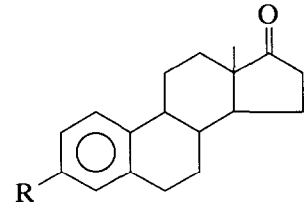
In this paper we describe the introduction of α-formyl-ethyl moiety into the estrene skeleton via homogeneous catalytic coupling and hydroformylation reactions.

2. Results and discussion

The 3-ethenyl-estra-1,3,5(10)-triene-17-one (**2**) was synthesized by a highly chemoselective palladium-catalysed reaction between vinyltributyltin and the triflate derivative **1a** (eqn. (1)). The isolated yield was 62%.



1a X = CF_3SO_2-
1b X = 4-$CH_3C_6H_4SO_2$-
1c X = 4-$BrC_6H_4SO_2$-
1d X = CH_3SO_2-



(1)

2 R = CH_2=CH-
3 R = 4-(CH_2=CH)$C_6H_4SO_3$-

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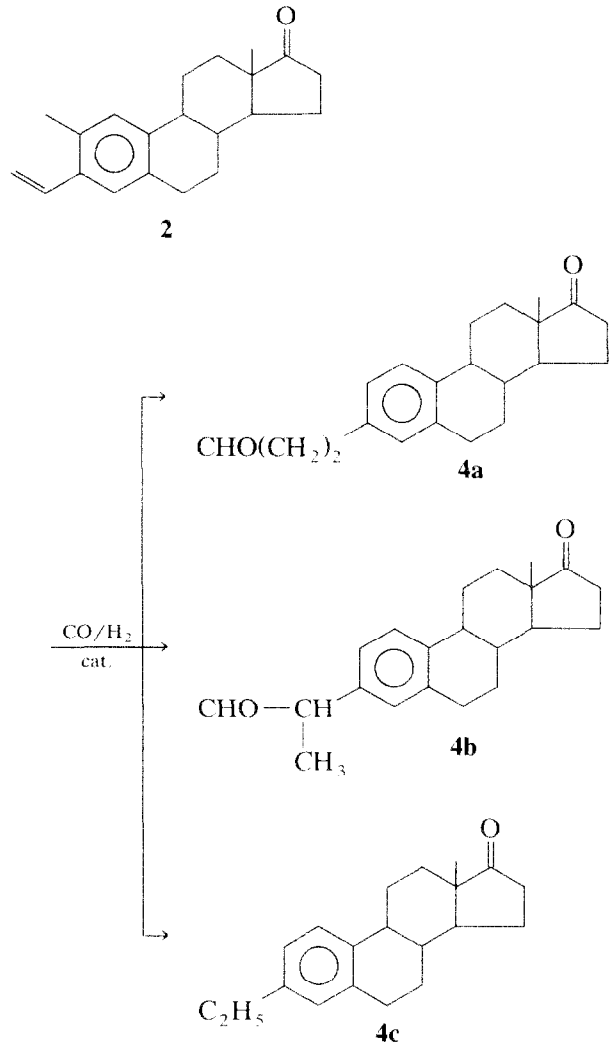
The reaction is strongly influenced by the leaving group. With "poorer" leaving groups no reaction occurred. The tosylate (**1b**) and mesylate (**1d**) did not react even under more severe conditions, and use of 4-bromobenzenesulfonate (**1c**) resulted in the formation of 3-(4'-ethenyl-benzenesulfonate)estr-1,3,5(10)-triene-17-one (**3**); no detectable displacement of the 4-bromobenzenesulfonate group took place showing the much greater reactivity of the bromoaryl bond towards the organotin reagent.

The styrenic estrogen (vinyl-derivative, **2**) was hydroformylated in the presence of phosphinerhodium and phosphineplatinum-tin(II) chloride catalysts. As expected, the formation of the formyl-products (linear and branched regioisomers, **4a** and **4b**, respectively) was accompanied by the hydrogenation of **2** to give 3-ethylestrone (**4c**) (eqn. (2)).

The chemoselectivity of the hydroformylation is high in all cases, resulting in formation of only a fairly small yield (8–21%) of the hydrogenated product (Table 1). The chemoselectivities are comparable with those obtained under similar conditions with styrene. The highest values were obtained with rhodium-catalysts containing bidentate phosphines.

Both in the presence of the Wilkinson-type rhodium-containing *in situ* catalyst, $[Rh(nbd)Cl]_2 + PPh_3$, and in that of preformed $PtCl(SnCl_3)[(R)$-PROPHOS] (PROPHOS = (*R*)-1,2-bis(diphenylphosphino)propane) or $PtCl(SnCl_3)[(S,S)$-CHIRAPHOS] (CHIRAPHOS = (2*S*,3*S*)-2,3-bis(diphenylphosphino)butane) the formation of the branched aldehyde is favoured. Surprisingly, the regioselectivity in the hydroformylation of **2** is much higher than in the case of simple vinyl aromatics [21], and this results in the formation of the more valuable product (**4b**) containing a new stereogenic centre (C-3'). With the rhodium-PROPHOS catalyst up to 92% regioselectivity was observed. The structure of **4b** closely resembles that of α-arylpropanals, possible intermediates on the way to the anti-



(2)

inflammatory agents (α-arylpropionic acids). The steroidal moiety serves as an aryl-substituent.

The platinum catalysts favour the formation of the

TABLE 1. Homogeneous hydroformylation of **2** in the presence of rhodium and platinum catalysts [a]

Catalyst	R.time (h)	Conv. [b] (%)	R_L [c] (%)	R_R [d] (%)	Ratio of the 3'-epimers [e]
$0.5\ [Rh(nbd)Cl]_2 + 2PPh_3$	10	> 98	79	85	> 98/2
$0.5\ [Rh(nbd)Cl]_2$ + (*R*)-PROPHOS	12	96	92	92	90/10
$0.5\ [Rh(nbd)Cl]_2$ + (2*S*,3*S*)-CHIRAPHOS	10	95	90	90	> 98/2
$PtCl(SnCl_3)[(R)$-PROPHOS]	20	> 98	81	81	> 98/2
$PtCl(SnCl_3)[(2S,3S)$-CHIRAPHOS]	20	96	85	83	> 98/2

[a] Reaction conditions: 0.025 mmol catalyst; 1 mmol substrate; $p(CO) = p(H_2) = 40$ bar; 100°C; toluene; PROPHOS = (*R*)-1,2-bis(diphenylphosphino)propane; CHIRAPHOS = (2*S*,3*S*)-2,3-bis(diphenylphosphino)butane; [b] (mol reacted **2**/mol initial **2**) · 100; determined by ^1H NMR; [c] chemoselectivity {(**4a** + **4b**)/(**4a** + **4b** + **4c**) · 100}; [d] regioselectivity {**4b**/(**4a** + **4b**) · 100}; [e] ratio of the two epimers determined by ^1H NMR.

linear (or less branched) aldehyde [21]. As expected, the regioselectivity is slightly lower with platinum catalysts, *i.e.* the yield of the linear aldehyde **4a** is increased, although the branched regioisomer still predominates, resulting in 81–83% regioselectivity.

The new stereogenic centre (C-3′) formed in the stereodifferentiating reaction is configurationally pure except when the PROPHOS-containing rhodium catalyst is used. The epimeric composition of the formyl-products was determined by ^{1}H and ^{13}C-NMR spectroscopy. The pairs of quartets at 3.58 and 3.64 ppm are assigned to the C*H*CH$_3$ protons of the two epimers. The branched aldehyde (**4b**) was chosen to be a pure epimer by chromatographic methods and by use of various NMR shift reagents.

The high asymmetric induction shows the importance of the estrene skeleton for chiral discrimination. The consecutive use of two highly selective homogeneous catalytic reactions yielded the pure formyl-enantiomer. This approach could be valuable for the synthesis of other functionalized steroids of practical importance.

3. Experimental section

3.1. Reagents

The catalytic precursors [Rh(nbd)Cl]$_2$ and the preformed platinum catalysts, PtCl(SnCl$_3$)(PROPHOS) and PtCl(SnCl$_3$)(CHIRAPHOS) were prepared as described previously [22,23]. Toluene was distilled under argon from sodium in the presence of benzophenone.

The ^{1}H and ^{13}C NMR spectra were recorded with CDCl$_3$ solutions containing TMS as internal standard on a Varian Unity 300 spectrometer. Samples were analyzed by use of a Hewlett Packard 5830A gas chromatograph with an SPB-1 column. The MS-spectra were obtained on a Hewlett Packard 5971A GC-MSD spectrometer.

3.2. Cross-coupling experiments

In a typical experiment a mixture of **1a** (1 mmol), vinyltributylstannane (1 mmol), Pd(PPh$_3$)$_4$ (0.02 mmol), lithium chloride (5 mmol) and a few crystals of ^{t}butylcatechol in dioxane was kept under argon at 110°C for 12 h. After 6 h an additional 0.02 mmol of Pd(PPh$_3$)$_4$ was added. The progress of the reaction was monitored by GLC and the product was purified after removal of the solvent by crystallization from methanol (yield: 174 mg; 62%).

3.3. Hydroformylation experiment

In a typical experiment a solution of 0.025 mmol catalyst in 15 ml of toluene was transferred under argon into a 100 ml stainless steel autoclave containing **2** (1 mmol). The autoclave was pressurized to 80 bar with a 1/1 CO/H$_2$ mixture, placed in a thermostated electric oven, and agitated with an arm shaker. After cooling and venting of the autoclave, the solution was evaporated to leave an oily residue which was analyzed by NMR spectroscopy. The products were separated by column chromatography on silica gel with petroleum ether and petroleum ether/ethylacetate = 8/1 as eluents. New compounds were characterized by ^{1}H-^{1}H COSY, ^{13}-C-^{1}H HETCOR, and DEPT NMR methods and mass spectroscopy.

3.4. Details of the products

3.4.1. 3-vinyl-estra-1,3,5(10)-triene-17-one (2)

^{1}H NMR (δ, CDCl$_3$): 7.25 (d, 8.1 Hz, 1H, C^2*H*); 7.21 (d, 8.1 Hz, 1H, C^1*H*); 7.13 (s, 1H, C^4*H*); 6.66 (dd, 11.1 Hz, 17.7 Hz, 1H, =C*H*C^3); 5.70 (d, 17.7 Hz, 1H, C*H*$_a$H$_b$ = CH); 5.19 (d, 11.1 Hz, 1H, CH$_a$*H*$_b$=CH); 2.92 (m, 2H, C^{16}*H*$_2$); 1.4–2.6 (m, 13H); 0.91 (s, 3H, C^{18}*H*$_3$); ^{13}C-NMR (δ, CDCl$_3$): 220.8 (*C*O); 139.6 (*C*^{3}); 136.7 (=*C*C^3); 136.6 (*C*^{5}); 135.3 (*C*^{10}); 126.9 (*C*^{1}); 125.6 (*C*^{2}); 123.7 (*C*^{4}); 113.2 (*C*H$_2$=CH); 50.6 (*C*^{9}); 48.0 (*C*^{13}); 44.5 (*C*^{14}); 38.2 (*C*^{8}); 35.9 (*C*^{16}); 31.7 (*C*^{6}); 29.5 (*C*^{15}); 26.6 (*C*^{7}); 25.8 (*C*^{11}); 21.7 (*C*^{12}); 13.9 (*C*^{18}); MS (*m*/*z*/rel.int.): 280/1000(M$^+$); 223/125.

3.4.2. 3-(4′-vinylphenylsulfonate)-estra-1,3,5(10)-triene-17-one (3)

^{1}H NMR (δ, CDCl$_3$): 7.81 (d, 8.4 Hz, 2H); 7.54 (d, 8.4 Hz, 2H); 7.16 (d, 8.4 Hz, 1H, C^1*H*); 6.80 (d, 2.4 Hz, 1H, C^4*H*); 6.76 (dd, 17.7 Hz, 11.1 Hz, 1H, CH$_2$=C*H*); 6.68 (dd, 2.4 Hz, 8.4 Hz, 1H, C^2*H*); 5.92 (d, 17.7 Hz, 1H, C*H*$_a$H$_b$=CH); 5.48 (d, 11.1 Hz, 1H, CH$_a$*H*$_b$=CH); 2.85 (m, 2H, C^{16}*H*$_2$); 1.3–2.55 (m, 13H, ring protons); 0.9 (s, 3H, C^{18}*H*$_3$).

3.4.3. 3-(2′-formylethyl)-estra-1,3,5(10)-triene-17-one (4a)

^{1}H NMR (as a mixture of **4a** / **4b** = 1/8) (δ, CDCl$_3$): 9.82 (t, 1.5 Hz, 1H, C*H*O); 2.8 (m, 2H, C*H*$_2$CHO); MS (*m*/*z*/rel.int.): 310/1000(M$^+$); 281/700(M$^+$ − CHO); 266/405 (M$^+$ − CHO − CH$_3$); 254/185 (M$^+$ − CHCH$_2$CHO).

3.4.4. 3-(1′-formylethyl)-estra-1,3,5(10)-triene-17-one (4b)

^{1}H NMR (δ, CDCl$_3$): 9.66 (d, 1.6 Hz, 1H, C*H*O); 7.31 (d, 7.1 Hz, 1H, C^2*H*); 7.05 (d, 7.1 Hz, 1H, C^1*H*); 6.94 (s, 1H, C^4*H*); 3.58 (q, 7.6 Hz, 1H, C*H*CHO); 2.9 (m, 2H, C^{16}*H*$_2$); 1.45–2.58 (m, 13H); 1.43 (d, 7.6 Hz, 3H, CHC*H*$_3$); 0.92 (s, 3H, C^{18}*H*$_3$); ^{13}C-NMR (δ, CDCl$_3$): 220.9 (*C*O); 201.4 (*C*HO); 139.4; 137.6; 135.4; 129.2; 126.4; 126.0; 52.8; 50.8; 48.2; 44.6; 38.4; 36.1;

31.8; 29.6; 26.7; 26.0; 21.9; 14.8 ($CHCH_3$); 14.1 (C^{18}); MS (m/z/rel.int.): 310/160 (M^+); 281/1000 (M^+ – CHO); 207/70; 117/110.

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