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Diastereoselective hydroformylation of Δ^4-steroids with rhodium–phosphite catalysts

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Abstract—The hydroformylation of two steroidal substrates, namely 17β-acetoxyandrost-4-ene **1** and 3β,17β-diacetoxyandrost-4-ene **2**, with a rhodium tris(*O-tert*-butylphenyl)phosphite catalyst was investigated. In both cases, the major reaction product was 4β-formyl-17β-acetoxy-5β-androstane **3**, which was isolated and characterized by X-ray diffraction and NMR techniques. This reaction is the first example of catalytic carbonylation to the β face of a steroid backbone. The effect of reaction temperature, the pressure at which the reaction was completed and the ligand:Rh ratio on the regio- and stereoselectivity of the reaction is also discussed.

1. Introduction

There is an increasing interest in developing new strategies to introduce functional groups into specific positions of steroidal nuclei in order to modulate their biological properties.[1,2] Hydroformylation is now a well established process in the production of fine chemicals for the introduction of an aldehyde functionality into complex molecules containing a carbon–carbon double bond.[3] However, the catalytic carbonylation of unsaturated steroids has been only scarcely reported compared with the equivalent reaction on other substrates. Recent work in this area used steroidal substrates containing an exocyclic olefin[4,5] or unsaturation at the D ring (the five-membered ring).[6–8] The stereochemistry of the major products revealed addition occurred from the α face of the steroid backbone. Furthermore, in the hydroformylation of 3β,17β-dihydroxyandrosta-5,16-diene, containing double bonds in both the D and B rings, only the D ring was carbonylated, while the more hindered double bond at the six-membered B ring remained intact.[7] The only two reports dealing with the carbonylation of a double bond on a six-membered ring of a steroid were published in the 1950s. These pioneering works describe the reaction of 3β-acetoxy-pregn-5-ene-20-one and 3β,20β-diacetoxy-pregn-5-ene under quite drastic conditions with *syn*-gas in the presence of cobalt catalysts. In both cases, the corresponding 6α-hydroxymethylpregnanes were obtained in 60% yield. Also, a *trans*-fusion of rings A and B was observed, which is the expected one for *cis*-addition of the formyl group and hydrogen to the α face of the steroid.[9,10] Since these works were reported, a number of very efficient hydroformylation catalysts have been developed, most of them based on rhodium and *P*-donor ligands.[11] Of these catalysts, tris(*O-tert*-butylphenyl)phosphite has been shown to form active rhodium catalysts for the hydroformylation of hindered olefins.[12–14]

We report herein the low pressure rhodium/tris(*O-tert*-butylphenyl)phosphite-catalyzed hydroformylation of two Δ^4-steroids, 17β-acetoxyandrost-4-ene **1** and 3β,17β-diacetoxyandrost-4-ene **2**. Both substrates contain a double bond at the same position of the A ring, for which carbonylation has not been previously explored.

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2. Results and discussion

2.1. Catalytic reactions

Substrate **1** was prepared in 80% yield by reduction of testosterone acetate with $NaBH_4$ in $CF_3COOH/AcOH/CH_3CN$.[15] Substrate **2** was synthesized in two steps from the same material: reduction with $NaBH_4$ in MeOH afforded 3β-hydroxy-17β-acetoxyandrost-4-ene[15] (74% yield), followed by acetylation with Ac_2O/py (60% yield).[16]

The catalyst was prepared in situ by reaction of $[Rh_2(\mu\text{-}OMe)_2(cod)_2]$ and tris(*O-tert*-butylphenyl)phosphite under CO/H_2 atmosphere. The hydroformylation of substrates **1** and **2** with this catalyst was then examined and the results of the study are collected in Table 1.

For substrate **1**, the major aldehyde product was found to be 4β-formyl-17β-acetoxy-5β-androstane **3** (Scheme 1). The product **3** was purified by chromatography on silica gel using dichloromethane/petroleum ether as eluent (1:1). Crystals suitable for X-ray diffraction were obtained by recrystallization from petroleum ether with a few drops of dichloromethane. The product was characterized by X-ray diffraction and NMR techniques.

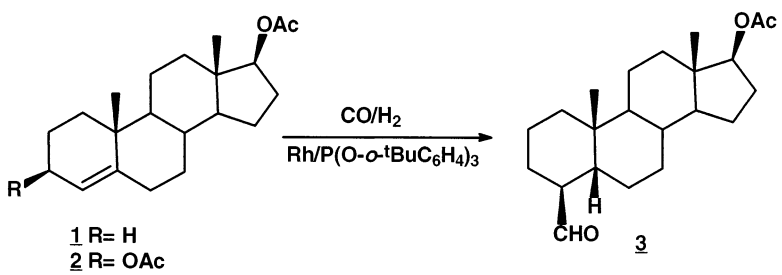
Aldehyde **3** is the expected regioisomer (i.e. the formyl group addition to the less substituted carbon) and it is formed by the reaction of the catalyst with the double bond to the β face of the steroidal skeleton. This is in contrast to that reported for the hydroformylation of Δ^5-steroids, which afforded α addition products.[9,10] Homogenous[17,18] and heterogenous[19,20] catalytic reactions involving Δ^4-steroids have been widely investigated. For these substrates, products of both the α and the β attack are obtained, depending on the catalyst and the substituents on the steroid. The existence of a stable conformation with a partially folded structure along the A and B ring-fusion bond has previously been invoked to explain formation of the β products.[21] This is probably the reason for the stereochemistry of the major product from the hydroformylation of **1**.

For substrate **1**, the *cis*-addition of the hydrogen and the formyl group over the double bond, with the formyl group in a 4β-position, produces the *cis*-fusion of rings A and B (i.e. 5β-H). Both, the formation of a *cis*-addition product, and the fact that only one further aldehyde product is observed (likely the 4α-formyl derivative), suggests that the reaction takes place by direct hydroformylation of Δ^4 double bond and not through previous isomerization of the substrate, for which a more complicated mixture of products would be expected. Furthermore, analysis of the reaction mixture at intervals through the catalytic process reveals the formation of variable amounts of isomers of substrate **1**. These isomeric products are hydroformylated only at the end of the reaction, with concomitant formation of small amounts of other aldehyde side products. The overall effect is a decrease in the regioselectivity of the reaction. It should be noted, however, that the ratio of the two initially formed aldehydes remains practically constant (ca. 7/3) throughout the reaction and that the hydroformylation of the isomerized products does not change the output of aldehyde **3**.

Table 1. Hydroformylation of steroids **1** and **2** with the $[Rh_2(\mu\text{-}OMe)_2(cod)_2]/P(O\text{-}o\text{-}^tBuC_6H_4)_3$ catalytic system[a]

Entry	Substrate	Temp. (°C)	Pressure (bar)	L:Rh	Time (h)	Conv.[b] (%)	Chem.[c] (%)	Aldehyde **3**[d] (%)
1	**1**	70	20	2.5	48	44	34	64
2	**1**	100	20	2.5	48	89	85	61
3	**1**	100	10	10	48	80	60	65
4	**1**	100	20	10	48	89	85	61
5	**1**	100	40	2.5	48	89	77	68
6	**2**	100	20	2.5	48	97	70	58
7[e]	**1**	100	20	2.5	48	60	78	60

[a] Reaction conditions: Substrate (1.26×10^{-3} mol) and Rh (1.26×10^{-4} mol) dissolved in toluene (6 mL).
[b] Calculated as a percentage of converted substrate.
[c] [Total aldehydes]/[olefin converted].
[d] [Aldehyde **3**]/[total aldehydes].
[e] S/Rh = 50.



Scheme 1.

The best yields of aldehyde **3** were obtained at 100°C and 20–40 bar pressure (entries 2, 4 and 5). At 120°C the reaction lacks reproducibility and no apparent improvement in the conversion was obtained, these observations are a result of catalyst decomposition under the reaction conditions. No significant effect on the activity or selectivity was observed when either the pressure or the molar ratio of ligand to metal was changed, except for a pressure of 10 bar, at which the chemoselectivity of the reaction decreased (entry 3).

It is noteworthy that hydroformylation of substrate **2** at 100°C and 20 bar pressure also produced the aldehyde **3** as the major component of the reaction mixture (entry 6). The isolated yield was similar to that obtained with substrate **1**. The formation of **3** could arise from the elimination of acetic acid after the hydroformylation, followed by the stereoselective hydrogenation of the unsaturated aldehyde at the α face of the steroid. A similar situation has been previously reported for allylic acetates derived from carbohydrates.[22] However, a path involving the formation of Rh-π-allyl intermediate cannot be completely excluded.[23] Studies to elucidate the mechanism of this reaction are underway.

2.2. X-Ray crystal structure of aldehyde 3

Fig. 1 shows the molecular structure of aldehyde **3** obtained by X-ray analysis.[24] Rings A and B have a *cis*-junction typical of a 5β epimer. This is revealed by the torsion angles C(19)–C(10)–C(5)–C(4) = 166.8(4)° and C(1)–C(10)–C(5)–C(6) = 176.2(3)°. As expected, the other ring junctions are *trans*-orientated. A twist around the C(13)–C(14) bond can also be seen in the five-membered ring. The distance between the two more distant terminal atoms, 0(1) and C(17B), is 12.03 Å.

2.3. NMR analysis of aldehyde 3

The assignment of most of the proton and carbon signals in the ^{1}H and ^{13}C NMR spectra of aldehyde **3** was achieved by using two-dimensional techniques. The results are collected in Table 2.

The proton correlations observed in the COSY spectrum between the aldehydic proton, methylene protons and a methynic proton are in agreement with the presence of a 4-formyl group on the androstane nucleus. These results and the analysis of the HETCOR spectrum allow assignment of the C(3), C(4) and C(5) carbon resonances (Fig. 2).

In the HMBC spectrum, the aldehydic proton shows connectivity with C(4) (δ = 48.2) and also a weak correlation with the carbon resonance of another methylene group (δ = 23.4), which has then been assigned to C(2). The signal for C(4)H shows connectivities with C(3) (δ = 26.9) and C(5) (δ = 42.4). The 19-methyl group shows connectivities with C(1) (δ = 36.9 or 37.0), C(9) (δ = 41.6), C(10) (δ = 35.0) and also with C(5) (δ = 42.4) (Fig. 3).

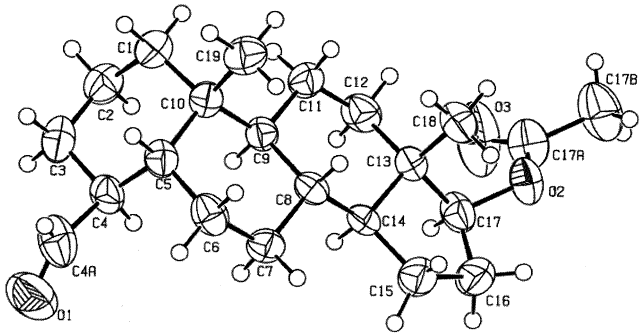


Figure 1. X-Ray structure of aldehyde **3**.

Table 2. ^{13}C and ^{1}H NMR data for aldehyde **3**

C	^{13}C (δ)	^{1}H (δ)
C1	36.9 or 37.0[a]	[b]
C2	23.4	[b]
C(3)	26.9	1.70–1.80 (m) C$\underline{H}_2$
C(4)	48.2	2.66–2.77 (m) C$\underline{H}$
C(5)	42.4	1.53–1.59 (m) C$\underline{H}$
C(8)	35.3	[b]
C(9)	41.6	1.20–1.40 (m) C$\underline{H}$
C(10)	35.0	–
C(13)	42.7	–
C(14)	50.7	1.00–1.20 (m) C$\underline{H}$
C(17)	82.8	4.6 (dd, J=9, J=7.9) C$\underline{H}$
O$\underline{C}$OCH$_3$	171.2	–
OCO$\underline{C}$H$_3$	21.2	2.04 (s) CH$_3$
CH$_3$ (18)	12.1	0.77 (s) CH$_3$
CH$_3$ (19)	23.9	1.01 (s) CH$_3$
CHO	205.5	9.41 (d, J=4.4) C$\underline{H}$O

[a] These resonances can be interchangeable
[b] These ^{1}H resonances were not assigned.

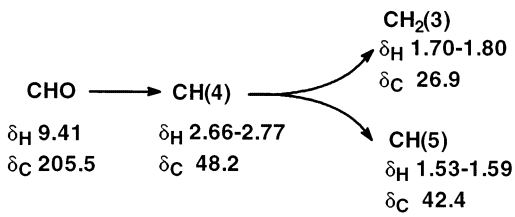


Figure 2. Correlations found in the COSY and HETCOR spectrum of **3** around the formyl group.

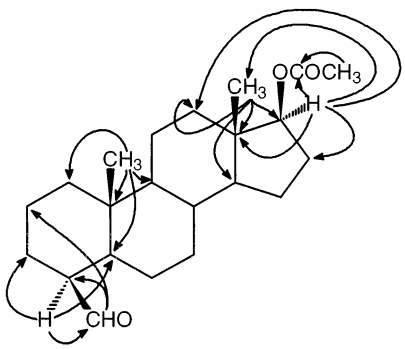


Figure 3. Main connectivity found in the HMBC spectrum of **3**.

The HMBC connectivities found for both the C(18)-CH_3 and C(17)H allowed the assignment of the majority of their neighboring carbon resonances. In the NOESY spectrum of aldehyde **3**, intense NOE cross peaks were observed between the resonances of the 19-methyl group and C(5)H, as well as between C(5)H and the aldehydic proton. This suggests that the three groups are on the same (β) face of the steroid plane, as is corroborated by the X-ray analysis. The absence of NOE cross peaks of C(4)H with C(5)H and the 19-methyl group, reinforces this hypothesis.

3. Conclusion

The system Rh-tris(*O-tert*-butylphenyl)phosphite catalyzes the hydroformylation of Δ^4 double bond of substrates **1** and **2**. The system is 68% selective in 4β-formyl-17β-acetoxy-5β-androstane **3**. This product was isolated from the reaction mixture in 50% yield and characterized by single crystal X-ray diffraction and double resonance NMR techniques. The hydroformylation reaction occurred preferentially at the β face of the steroid nucleus forming a new steroid with *cis*-fusion of A and B rings.

4. Experimental

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions on a Bruker AMX 300 spectrometer. ^1H assignments were made using 2D COSY and NOESY (mixing time of 800 ms) experiments, while ^{13}C assignments were made using HETCOR and HMBC (delays for long-range J C/H couplings were optimized for 7 Hz) experiments. GC and GC–MS were carried out on HP-5890 and HP-G1800A apparatus, both equipped with capillary HP5 columns. Reported melting points are not corrected.

$[Rh_2(\mu\text{-OMe})_2(cod)_2]$ and tris-(*O-tert*-butylphenyl)phosphite were synthesized by slightly modified procedures with respect to those described in the literature.[12,25]

4.1. General procedure for hydroformylation reactions

The appropriate quantities of substrate, tris-(*O-tert*-butylphenyl)phosphite, $[Rh_2(\mu\text{-OMe})_2(cod)_2]$ and a stirring bar were introduced in a glass vessel. This was then closed in the autoclave, and the system was purged by three cycles of vacuum and *syn*-gas. Being the reactor in vacuum, toluene was introduced through the inlet cannula. The reactor was pressurized with *syn*-gas at 40 bar at the working temperature for 45 minutes. After this incubation period, the autoclave was set to the desired pressure. Conversions and selectivities were determined throughout the reaction by gas chromatography analysis of aliquots of the mixture.

4.2. 17β-Acetoxyandrost-4-ene-3-one[26]

Montmorillonite (10 g) and Ac_2O (6.0 mL, 63 mmol) were added to a solution of testosterone (2.00 g, 6.93 mmol) in CH_2Cl_2 (200 mL) and the reaction mixture was refluxed overnight. Montmorillonite was removed by filtration and the resulting filtrate was washed twice with saturated aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$ and then evaporated. The crude product was recrystallized from CH_2Cl_2–petroleum ether–ethanol to produce a white crystalline material (1.66 g, 72%); mp 139–141°C (Lit.,[26] 139–140°C); ^1H NMR: δ 0.80 (s, 3H, C(18)Me), 1.15 (s, 3H, C(19)Me), 2.1 (s, 3H, CH_3COO), 4.56 (dd, $J=8.7$ Hz, $J=8.0$ Hz, 1H, C(17)H), 5.69 (s, 1H, C(4)H); ^{13}C NMR: δ 82.4 (C17), 123.9 (C4), 125.8 (C5), 171.1 (O$\underline{C}$OCH$_3$), 199.4 (C3).

4.3. 17-β-Acetoxyandrost-4-ene 1[15]

A mixture of CF_3COOH (1.8 mL), CH_3COOH (1.8 mL) and CH_3CN (1.8 mL), and $NaBH_4$ (0.30 g, 7.93 mmol) were added to an ice-cooled solution of 17β-acetoxyandrost-4-ene-3-one (0.50 g, 1.51 mmol) in CH_2Cl_2 (10 mL). After stirring for 10 h, aqueous $NaHCO_3$ was added dropwise until the pH of the mixture was 7. The mixture was extracted with CH_2Cl_2 and the organic layer washed with H_2O and dried over $MgSO_4$. The white solid obtained after evaporation of the solvent was recrystallized from CH_2Cl_2–petroleum ether–ethanol to afford the product as a crystalline material (0.38 g, 80%); mp 95–97°C (Lit.,[15] 97°C); ^1H NMR: δ 0.80 (s, 3H, C(18)Me), 1.02 (s, 3H, C(19)Me), 2.05 (s, 3H, CH_3COO), 4.58 (dd, $J=9$, $J=7.7$ Hz, 1H, C(17)H,), 5.30 (m, 1H, C(4)H); ^{13}C NMR: 82.8 (C17), 119.3 (C4), 144.7 (C5), 171.0 (O$\underline{C}$OCH$_3$); MS-EI: m/z 316 (M^+, 26%), 301 (4%), 256 (14%), 241 (34%), 146 (34%), 133 (24%), 93 (54%), 91 (45%), 79 (39%), 55 (23%), 43 (100%).

4.4. 17β-Acetoxy-3β-hydroxyandrost-4-ene[15]

A solution 17β-acetoxyandrost-4-ene-3-one (4.00 g, 12.1 mmol) in methanol (50 mL) was treated with $NaBH_4$ (3.00 g, 79.3 mmol) at 0°C for 2 h. AcOH (2.0 mL) was then added to destroy the excess of $NaBH_4$ and the mixture was poured into water. The product was extracted with ethyl acetate. The combined extracts were washed with water and dried over Na_2SO_4. The solvent was evaporated under vacuum and the crude was recrystallized to give white needles of 3β-hydroxy-17β-acetoxyandrost-4-ene (2.95 g, 74%); mp 135–136°C (Lit.,[15] 135–136°C); ^1H NMR: δ 0.77 (s, 3H, C(18)Me), 1.02 (s, 3H, C(19)Me), 2.01 (s, 3H, CH_3COO), 4.12 (m, 1H, C(3)H), 4.54 (dd, $J=7.9$ Hz, $J=10.0$ Hz, 1H, C(17)H), 5.25 (m, 1H, C(4)H); ^{13}C NMR: δ 67.8 (C3), 82. 7 (C17), 123.5 (C4), 147.1 (C5), 171.2 (O$\underline{C}$OCH$_3$).

4.5. 3β,17β-Diacetoxyandrost-4-ene 2[16]

3β-Hydroxy-17β-acetoxyandrost-4-ene (0.50 g, 1.51 mmol) was dissolved in a mixture of freshly distilled pyridine (1.0 mL, 12 mmol) and Ac_2O (2.5 mL, 26 mmol). After the complete disappearance of starting material (as indicated by TLC), the reaction mixture was washed with an aqueous saturated solution of $CuCl_2$, until no color change in the aqueous layer was observed, then with 10% HCl (aq.), a saturated solution

of $NaHCO_3$, and finally with water. The organic layer was dried over $MgSO_4$ and the solvent evaporated under vacuum. The resulting white solid was recrystallized from CH_2Cl_2–petroleum ether–ethanol to afford the crystalline product (0.34 g, 60%); mp 110–113°C (Lit.,[16] 101–102°C); ^1H NMR: δ 0.81 (s, 3H, 18-Me), 1.07 (s, 3H, C(19)Me), 2.04 (s, 3H, CH_3COO), 2.05 (s, 3H, CH_3COO), 4.58 (dd, 1H, C(17)H, $J=9$ Hz, $J=7.8$ Hz), 5.23 (m, 1H, C(4)H), 5.22 (m, 1H, C(3)H); ^{13}C NMR: δ 70.8 (C3), 82.7 (C17), 119.2 (C4), 149.1 (C5), 171.0 ($OCOCH_3$), 171.2 ($OCOCH_3$); MS-EI: m/z 374 (M^+), 314 (36%), 239 (19%), 146 (33%), 106 (52%), 91 (74%), 81 (30%), 55 (22%), 43 (100%).

4.6. 4β-Formyl-17β-acetoxy-5β-androstane 3

This product was synthesized by catalytic hydroformylation using the general procedure described above. The autoclave was charged with **1** (0.40 g, 1.26 mmol), tris-(*O-tert*-butylphenyl)phosphite (0.031 g, 0.063 mmol) and (0.006 g, 0.025 mmol) of $[Rh_2(\mu\text{-}OMe)_2(cod)_2]$ and toluene (6 mL). When the catalytic reaction was stopped, the reactor was cooled and depressurized. After evaporation of the toluene, the mixture of aldehydes was isolated by preparative chromatography (silica, petroleum ether–CH_2Cl_2 1:1). Finally, the aldehyde **3** was crystallized from a solution of petroleum ether–CH_2Cl_2 to give a white crystalline material (0.22 g, 50%); mp 112–114°C; ^1H and ^{13}C NMR are collected in Table 2; MS-EI: m/z 346 (M^+, 29%), 286 (13%), 201 (43%), 149 (27%), 105 (43%), 95 (43%), 43 (100%); $[\alpha]_D=+20$ (c 1, $CHCl_3$). Anal. calcd for $C_{22}H_{34}O_3$: C, 76.37; H, 9.90. Found: C, 76.59; H, 9.70%.

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