Available online at www.sciencedirect.com
ScienceDirect
Journal of Molecular Catalysis A: Chemical 275 (2007) 121–129
JOURNAL OF MOLECULAR CATALYSIS A: CHEMICAL
www.elsevier.com/locate/molcata

Hydroformylation of hindered double bonds of natural products with rhodium catalysts: The effect of 3-acetoxy substituent

Andreia F. Peixoto [a], Mariette M. Pereira [a,*], Artur M.S. Silva [b], Cláudia M. Foca [c], J. Carles Bayón [c,*], Maria José S.M. Moreno [d], Ana Matos Beja [e], José A. Paixão [e], Manuela Ramos Silva [e]

[a] *Departamento de Química, Universidade de Coimbra, 3004-535 Coimbra, Portugal*
[b] *Departamento de Química, Universidade de Aveiro, 3810-193 Aveiro, Portugal*
[c] *Departament de Química, Universitat Autónoma de Barcelona, Bellaterra, 08193 Barcelona, Spain*
[d] *CEF, Faculdade de Farmácia, Universidade de Coimbra, 3000-295 Coimbra, Portugal*
[e] *Departamento de Física, Universidade de Coimbra, 3004-516 Coimbra, Portugal*

Received 13 April 2007; received in revised form 22 May 2007; accepted 24 May 2007
Available online 31 May 2007

Abstract

The hydroformylation of Δ^4- and Δ^5-steroids, namely cholest-4-ene (**1**), 3β-acetoxycholest-4-ene (**2**), 3β-acetoxycholest-5-ene (**3**), and 3β-acetoxypregn-5-en-20-one (**4**), was studied using rhodium catalysts modified with P-donor ligands containing electron withdrawing substituents, such as tris(*o-tert*-butylphenyl)phosphite, tris(*o*-trifluoromethylphenyl)phosphine and tris(*p*-trifluoromethylphenyl)phosphine. The effect of temperature, pressure and ligand/Rh molar ratios on the regio- and stereoselectivity of the reaction were studied. Under the reaction conditions assayed, only the Δ^4-steroids **1** and **2** are hydroformylated, producing the 4-formyl derivatives with 100 % regioselectivity and 70 and 60 % stereoselectivity for the β isomer, respectively. Δ^5-Steroids **3** and **4** either did not react or produced traces of products from the isomerization of the double bond. Among the three catalysts used, only the Rh/tris(*o-tert*-butylphenyl)phosphite was able to catalyze the hydroformylation of Δ^4-steroids. The two new formyl steroids obtained from **1**, 4-formyl-5α-*H*-cholestane (**6**) and 4-formyl-5β-*H*-cholestane (**7**), were isolated as their acetal derivatives and fully characterized by 2D NMR techniques. The structure of the acetal arising from the minor aldehyde product of the reaction was further corroborated by X-ray analysis. The mechanism of the reaction for the conversion of 3β-acetoxycholest-4-ene **2** into **7** was investigated, through the hydroformylation of (1*R*)-(−)-myrtenyl acetate (**5**) as a cyclic allylic acetate model. The results show that the reaction does not take place through an allylic intermediate, but that the major aldehyde obtained from **2** undergoes AcOH elimination followed by stereoselective hydrogenation of the α,β-unsaturated aldehyde, leading to **7**.

Keywords: Hydroformylation; Steroids; Cholest-4-ene; 3β-Acetoxycholest-4-ene; 3β-Acetoxycholest-5-ene; 3β-Acetoxypregn-5-en-20-one; Myrtenyl acetate

1. Introduction

Inhibition of the human steroid 5-α-reductase with consequent suppression of the 5α-dihydrotestosterone biosynthesis has become an important pharmacological strategy for the treatment of prostatic cancer and other androgen dependent diseases [1]. Previous work on the steroid enzyme inhibitors [2,3] showed that the design of new compounds might involve the introduction of an electron withdrawing substituent into the 4-position of the steroid nucleus. In this context we have undertaken a study to develop the synthesis of new 4-formyl steroids [4]. The relevance of transition-metal catalysed reactions in steroid synthesis has been recently reviewed by Kollár [5]. Classic formyl steroid synthesis involves several steps, namely the coupling of a triflate group with an olefin catalysed by palladium salts, followed by ozonolysis [6].

Hydroformylation is now a well-established process for the direct introduction of formyl groups onto internal and external double bonds, and its use as a potential method for organic synthetic application is progressively growing [7–10]. The introduction of formyl groups onto the internal double bond of the steroid nucleus *via* non-modified cobalt cat-

* Corresponding author. Tel.: +351 239854474; fax: +351 239827703.
E-mail address: mmpereira@qui.uc.pt (M.M. Pereira).

1381-1169/$ – see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.molcata.2007.05.035

alyzed hydroformylation was reported in the fifties by Pike [11]. Later on, the hydroformylation and hydroesterification of less hindered 17-double bond in different steroidal substrates was developed by Toros, using rhodium-phosphine [12] and palladium-phosphine [13,14] modified catalysts. Recently our group reported the first efficient diastereoselective hydroformylation of a Δ^4-androstene derivative, using a rhodium-phosphite catalyst, which allowed the one-step synthesis of a new 4β-formyl-androstane [4]. In spite of the potentialities of this synthetic methodology, little information is available about its applicability in the chemistry of steroids.

In this paper we extend our previous work in this area to the investigation of the hydroformylation reaction of a different group of unsaturated steroids (cholestane and pregnane series). We also study the hydroformylation reaction of the monoterpene (1*R*)-(−)-myrtenol, to evaluate the scope and limitations of the rhodium catalysed hydroformylation in this type of substrates. With these studies we also provide conclusive evidence for the mechanism of hydroformylation of Δ^4-steroids containing a 3β-acetoxy substituent.

2. Experimental section

2.1. General

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions on Bruker 300 and 500 spectrometers, operating at 300.13 and 500.13 MHz, respectively for ^{1}H and at 75.47 and 125.76 MHz for ^{13}C. ^{1}H Assignments were made using 2D COSY and NOESY (mixing time of 800 ms) experiments, while ^{13}C assignments were made using 2D HSQC and HMBC experiments (long range C/H coupling constants were optimised to 7 Hz).

GC was carried out on Agilent-6890 and GC–MS was carried out on HP-G1800A and HP-5973 mass selective detector apparatus, equipped with capillary HP5 columns.

$[Rh_2(\mu\text{–}OMe)_2(cod)_2]$ [15] and tris(*o-tert*-butylphenyl) phosphite [16] were synthesized by slightly modified procedures with respect to those described in the literature.

2.2. Substrates

Cholest-4-en-3-one, 3β-hydroxypregn-5-en-20-one, 3β-hydroxycholest-5-ene and 1*R*-(−)-myrtenol were purchased from Aldrich.

2.2.1. Cholest-4-ene (*1*)

A mixture of CF_3COOH (14 mL), $(CH_3CO)_2O$ (14 mL), CH_3CN (14 mL) and $NaBH_4$ (2.3 g, 59.7 mmol) were added to an ice-cooled solution of cholest-4-ene-3-one (3.8 g, 9.9 mmol) in CH_2Cl_2 (25 mL). After stirring for 5 h, aqueous $NaHCO_3$ was added dropwise until the solution reached pH 7.0. 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 in dichloromethane/hexane/ethanol (10:0.5:0.5) to afford the product as a crystalline material (2.7 g, 74%); mp: 82–85 °C (Lit., [17] 78–79 °C); EIMS: $m/z = 370$ (M^+); ^{1}H NMR, ppm: $\delta = 0.73$ (s, 3H, 18-CH_3), 0.91 (dd, $J = 6.6$, $J = 1.4$ Hz, 26-CH_3), 0.96 (d, $J = 6.6$ Hz, 27-CH_3), 0.97 (s, 3H, 21-CH_3), 1.06 (s, 3H, 19-CH_3), 5.35 (m, 1H, 4-C*H*), ^{13}C NMR: $\delta = 118.9$ (C-4), 145.2 (C-5); $C_{27}H_{46}$: calcd C 87.49, H 12.51; found C 87.62, H 12.38.

2.2.2. 3β-Acetoxycholest-4-ene (*2*)

3-Hydroxycholest-4-ene was synthesized by cholest-4-en-3-one (300.0 mg, 0.8 mmol) reduction using $NaBH_4$ (30.0 mg, 0.8 mmol) in CH_3OH (7 mL). The reaction was controlled by TLC using ethyl acetate/hexane (1:2) as eluent. After 1 h the reaction was stopped, the methanol was evaporated and the crude product taken up in dichloromethane (100 mL) and washed with water (three times). After drying with $MgSO_4$ and filtration, the complete evaporation of the solvent was done. A mixture of β/α hydroxy isomers was obtained (74:26) after recrystallization in ethanol (296.0 mg, 95% yield). mp: 122–125 °C; ^{1}H NMR, ppm: $\delta = 0.68$ (d, 3H, $J = 1.7$ Hz, CH_3-18), 0.86 (dd, 6H, $J = 6.6$, $J = 1.4$ Hz, CH_3-26 and CH_3-27), 0.90 (d, 3H, $J = 6.5$ Hz, CH_3-21), 1.05 (s, 3H, CH_3-19), 4.07 (m, H, H-3α), 4.14 (m, H, H-3β), 5.27 (d, H, $J = 1.4$ Hz, H-4β), 5.45 (dd, H, $J = 4.8$, $J = 1.4$ Hz, H-4α). $C_{27}H_{46}O$: calcd C 83.87, H 11.99; found C 83.18, H 14.79.

The mixture of the β/α 3-hydroxycholest-4-ene (296.0 mg, 0.8 mmol) obtained in the procedure described above, was dissolved in dry pyridine (0.5 mL, 12.0 mmol) and $(CH_3CO)_2O$ (1.3 mL, 13.3 mmol). The reaction was monitored by TLC. After the complete disappearance of starting material, the product was washed with an aqueous saturated solution of $CuSO_4$, until no colour change in the aqueous layer was observed, then it was also washed with 10% HCl (aq) and finally with a saturated solution of $NaHCO_3$. The organic layer was dried over $MgSO_4$ and the solvent evaporated under vacuum. The crude was recrystallized (four times) with dichloromethane/hexane (1:5) to afford the crystalline 3β-acetoxycholest-4-ene (**2**) (159.5 mg, 49% yield). EIMS: $m/z = 428$ (M^+); ^{1}H NMR: $\delta = 0.68$ (s, 3H, 18-CH_3), 0.85 (d, $J = 6.5$ Hz, 2× 3H, 26,27-CH_3), 0.90 (d, $J = 6.5$ Hz, 3H, 21-CH_3), 1.06 (s, 3H, 19-CH_3), 2.05 (s, 3H, CH_3COO), 5.22 (m, 2× 1H, 3-C*H* and 4-C*H*); ^{13}C NMR: $\delta = 70.9$ (C-3), 118.8 (C-4), 149.7 (C-5), 170.9 (O*C*OCH$_3$); $C_{29}H_{48}O_2$: calcd C 81.25, H 11.29, found C 81.38, H 11.13.

2.2.3. 3β-Acetoxycholest-5-ene (*3*)

Montmorillonite (12.0 g) and $(CH_3CO)_2O$ (4.6 mL, 49.0 mmol) were added to a solution of 3β-hydroxycholest-5-ene (2.0 g, 5.2 mmol) in CH_2Cl_2 (200 mL). After the complete disappearance of starting material (monitored by TLC), the montmorillonite was removed by filtration and the resulting filtrate was washed with a saturated solution of $NaHCO_3$, until the solution adjusted to pH 7.0. The organic layer was dried over $MgSO_4$ and then evaporated. The crude product was recrystallized from dichloromethane/hexane/ethanol (10:0.5:0.5) to afford the crystalline product (1.99 g, 90% yield); mp: 108–110 °C; EIMS: $m/z = 428$ (M^+); ^{1}H NMR: $\delta = 0.67$ (s, 3H, 18-CH_3), 0.85 (d, $J = 7.5$ Hz, 2× 3H, 26,27-CH_3), 0.91 (d, $J = 6.5$ Hz, 3H, 21-CH_3), 1.02 (s, 3H, 19-CH_3), 2.04 (s, 3H, CH_3COO), 2.31 (d, $J = 7.7$ Hz, 2H, 4-CH_2), 4.60 (m, 1H, 3-C*H*), 5.37 (m, 1H, 6-C*H*); ^{13}C NMR: $\delta = 122.6$ (C-5), 139.6

(C-6), 170.5 ($OCOCH_3$); $C_{29}H_{48}O_2$: calcd C 81.25, H 11.29, found C 80.86, H 11.25.

2.2.4. 3β-Acetoxypregn-5-en-20-one (4)

3β-Acetoxypregn-5-en-20-one (**4**) was synthesized by reaction of 3β-hydroxypregn-5-en-20-one (1.0 g, 3.2 mmol) in dry pyridine (5 mL, 62.1 mmol) and $(CH_3CO)_2O$ (3 mL, 31.7 mmol) using the procedure described above in Section 2.2.2. The reaction was monitored by TLC. The resulting white solid was recrystallized from dichloromethane/hexane/ethanol (10:0.5:0.5) to afford the crystalline product (0.97 g, 85%); mp: 146–148 °C (Lit., [18] 149–150 °C); EIMS: $m/z = 358$ (M^+); ^{1}H NMR: $\delta = 0.63$ (s, 3H, 18-CH_3), 1.02 (s, 3H, 19-CH_3), 2.04 (s, 3H, CH_3COO), 2.13 (s, 3H, 21-CH_3), 2.55 (t, $J = 6$ Hz, 1H, 17-CH), 4.61 (m, 1H, 3-CH), 5.38 (m, 1H, 6-CH), ^{13}C NMR: $\delta = 122.3$ (C-5), 139.6 (C-6), 170.5 ($OCOCH_3$), 209.6 (C-20); $C_{23}H_{34}O_3$: calcd C 77.05, H 9.56, found C 76.67, H 9.53.

2.2.5. (1R)-(−)-Myrtenyl acetate (5)

The (1*R*)-(−)-myrtenol (6.0 g, 38.5 mmol) was dissolved in a mixture of freshly dried pyridine (6 mL, 756.6 mmol) and $(CH_3CO)_2O$ (9 mL, 386.2 mmol). The reaction evolution was monitored by GC. After complete disappearance of the starting materials, the work-up was done according to the procedure described in the Section 2.2.2. The (1*R*)-(−)-myrtenyl acetate was isolated by silica gel column preparative chromatography using dichloromethane as eluent. After evaporation of the solvent the (1*R*)-(−)-myrtenyl acetate (**5**) was obtained as an oil (7.1 g, 93%).

The assignments obtained for most of the protons in the ^{1}H NMR spectrum are in accordance with the assignments published by Lee [19] on the characterization of the related structure of myrtenol.

^{1}H NMR: $\delta = 0.825$ (s, 3H, 9-CH_3), 1.18 (d, $J = 8.6$ Hz, 1H, 7-CH_2), 1.30 (s, 3H, 8-CH_3), 2.04 (s, 3H, –OCH_3), 2.06 (m, 1H, 5-CH), 2.11 (dd, $J = 1.4$ and 5.6 Hz, 1H, 1-CH), 2.27 (dt, $J = 2.5$ and 6.9 Hz, 2H, 4-CH_2), 2.41 (d, $J = 8.6$ Hz, 1H, 7-CH_2), 4.43 (d, $J = 7.1$ Hz, 2H, CH_2O).

2.3. General hydroformylation procedure

The autoclave charged with the appropriate amounts of phosphorus ligand and $[Rh_2(\mu\text{-OMe})_2(cod)_2]$ was purged by three cycles of vacuum and *syn-gas*. Being the reactor in vacuum, toluene was introduced. Then, the reactor was pressurized with *syn-gas* at 40 bar at the working temperature during 45 min. After this incubation period, the pressure was released and the substrate, dissolved in the minimum amount of toluene, was introduced through the inlet cannula. Then, the pressure was set to the desired value for the catalytic experiment. The conversion and selectivity along the reaction were determined by gas chromatography analysis of aliquots from the reaction mixture. The same procedure was used for the deuteroformylation experiments, replacing H_2 by D_2.

2.3.1. 4β-Formyl-5β-H-cholestane (7)

This product was synthesized by catalytic hydroformylation using the general procedure described above. $[Rh_2(\mu\text{-OMe})_2(cod)_2]$ (2.2×10^{-2} mmol) and tris(*o-tert*-butylphenyl)phosphite (5.4×10^{-2} mmol) were incubated in toluene (4 mL). Then the autoclave was charged with cholest-4-ene **1** (0.4 g, 1.1 mmol) dissolved in toluene (2 mL). When the catalytic reaction was stopped, the reactor was cooled and depressurised. After evaporation of the toluene, the mixture of 4α-formyl-5α-*H*-cholestane (**6**) and 4β-formyl-5β-*H*-cholestane (**7**) were purified and isolated by silica gel column chromatography using hexane as eluent (0.2 g, 70% yield). This mixture was resubmitted to a column chromatography using the same conditions and the major product of the reaction, 4β-formyl-5β-*H*-cholestane (**7**), was isolated (51.0 mg, 22% yield).

^{1}H NMR: $\delta = 0.64$ (s, 3H, 18-CH_3), 0.85–0.89 (s, 6H, 26,27-CH_3), 0.90 (s, 3H, 21-CH_3), 0.93–1.00 and 1.80–1.85 (m, 2H, 1-CH_2), 0.97–1.40 (m, 2H, 22-CH_2), 0.99 (s, 3H, 19-CH_3), 1.03–1.13 (m, 2× 1H, 14,17-CH), 1.04–1.09 and 1.40–1.46 (m, 2H, 23-CH_2), 1.06–1.26 (m, 2H, 24-CH_2), 1.10–1.20 (m, 2H, 11-CH_2), 1.12–1.16 and 1.96–1.99 (m, 2H, 12-CH_2), 1.26–1.30 and 1.73–1.76 (m, 2H, 3-CH_2), 1.26–1.34 (m, 1H, 9-CH), 1.35–1.45 (m, 1H, 20-CH), 1.48–1.54 (m, 1H, 25-CH), 1.53–1.57 (m, 1H, 5-CH), 1.87–1.94 (m, 2H, 15-CH_2), 2.69–2.74 (m, 1H, 4-CH), 9.41 (d, $J = 2.7$ Hz, 1H, 4A-CHO). ^{13}C NMR: $\delta = 12.0$ (C-18), 18.7 (C-21), 20.9 (C-15), 22.5 (C-26), 22.8 (C-27), 23.8 (C-11), 24.2 (C-19), 26.0 (C-23), 27.0 (C-3), 28.0 (C-25), 35.5 (C-20), 36.2 (C-22), 36.9 (C-1), 39.5 (C-24), 40.2 (C-12), 41.6 (C-9), 42.6 (C-5), 48.3 (C-4), 56.3 (C-17), 56.5 (C-14), 205.7 (C-4A).

2.3.2. Acetal synthesis (9, 10)

The mixture of aldehydes **6** and **7** (0.2 g, 0.6 mmol), 2,2-dimethyl-1,3-propanediol (845.4 mg, 8.1 mmol) and *p*-toluenesulfonic acid monohydrate (14.4 mg, 0.076 mmol) were added to toluene (60 mL). This solution was refluxed during 10 h using a Dean-Stark apparatus. After the work-up, the mixture of acetals **9** and **10** were obtained in 80% yield (0.2 g, 0.5 mmol). Two products were isolated by silica gel column chromatography using hexane as eluent and the remaining amount was isolated as a mixture of **9** and **10**. After recrystallization with dichloromethane:hexane (1:5), 4α-(5-dimethyl-1,3-dioxan-2-yl)-5α-*H*-cholestane (**9**) (33.0 mg, 55%) and 4β-(5-dimethyl-1,3-dioxan-2-yl)-5β-*H*-cholestane (**10**), (21.6 mg, 15%) were obtained as crystalline products.

2.3.2.1. 4α-(5-Dimethyl-1,3-dioxan-2-yl)-5α-H-cholestane (9).

mp: 161–164 °C. $[\alpha]_D^{25} = +15$ (c 1, $CHCl_3$) CIMS: $m/z = 485$ (M–H). ^{1}H NMR: $\delta = 0.64$ (s, 3H, 18-CH_3), 0.70 (s, 3H, C$H_{3\text{acetal}}$), 0.79 (s, 3H, 19-CH_3), 0.86 (d, $J = 6.6$ Hz, 2× 3H, 26,27-CH_3), 0.89 (d, $J = 6.6$ Hz, 3H, 21-CH_3), 0.93–1.00 and 1.80–1.85 (m, 2H, 1-CH_2), 0.97–1.40 (m, 2H, 22-CH_2), 1.03–1.13 (m, 2× 1H, 14,17-CH), 1.04–1.09 and 1.40–1.46 (m, 2H, 23-CH_2), 1.06–1.26 (m, 2H, 24-CH_2), 1.10–1.20 (m, 2H, 11-CH_2), 1.12–1.17 and 1.95–2.00 (m, 2H, 12-CH_2), 1.16 (s, 3H, C$H_{3\text{acetal}}$), 1.26–1.30 (m, 2H, 3-CH_2), 1.26–1.34 (m, 1H, 9-CH), 1.35–1.45 (m, 1H, 20-CH), 1.48–1.54 (m, 1H,

25-C*H*), 1.52–1.55 (m, 1H, 4-C*H*), 1.53–1.57 (m, 1H, 5-C*H*), 1.87–1.94 (m, 2H, 15-CH_2), 3.36 (d, J = 10.9 Hz, 2H, C$H_{2acetal}$), 3.42–3.59 (d, J = 10.9 Hz, 2H, C$H_{2acetal}$), 4.49 (d, J = 2.2 Hz, 1H, 4A-C*H*). ^{13}C NMR: δ = 12.0 (C-18), 12.9 (C-19), 18.6 (C-21), 20.9 (C-15), 21.8 (C$H_{3acetal}$), 22.6 (C$H_{3acetal}$), 22.8 (C-26) and (C-27), 23.8 (C-11), 25.0 (C-3), 26.0 (C-23), 28.0 (C-25), 35.8 (C-20), 36.1 (C-22), 38.4 (C-1), 39.5 (C-24), 40.1 (C-12), 40.8 (C-4), 46.8 (C-9), 54.5 (C-5), 56.2 (C-17), 56.5 (C-14), 77.3 (2× C$H_{2acetal}$), 102.3 (C-4A). *X-ray crystallography* crystal data: $C_{33}H_{58}O_2$, M = 486.79, monoclinic, a = 15.7791(17) Å, b = 6.046(3) Å, c = 17.1855(15) Å, β = 107.888(8)°, V = 1560.3(9) Å^3, T = 293(2) K, space group $P2_1$, Z = 2, μ(Cu Kα) = 0.463 mm^{-1}, ρ = 1.036. Data collection: Enraf-Nonius Mach3, Cu Kα, graphite monochromator, transparent crystal size (0.17 mm × 0.16 mm × 0.04 mm). Five thousand nine hundred and fourty-five reflections measured in the θ range 2.70–72.5, $-19 < h < 18$, $-7 < k < 7$, $0 < l < 21$, of which 3188 unique (R_{int} = 0.038). ψ-Scan absorption correction with 0.988 and 0.920 maximum and minimum transmission factor. Structural analysis and refinement: all 3188 unique reflections were used for direct methods structure determination (with program SHELX) and full matrix least-squares refinement (with program SHELXL) with anisotropic thermal parameters for all ordered non-H atoms [20]. Atoms C24, C25 and C27 were refined over two positions with isotropic thermal parameters. H atoms were placed at calculated idealized positions and refined as riding atoms, data-to-parameter ratio 10. The final R (F^2) was 0.0513 (for $I > 2\sigma(I)$) and $wR(F^2)$ was 0.1582 (for all reflections). CCDC 651606 [21] contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at http://www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223/336 033 (internat.); e-mail: deposit@ccdc.cam.ac.uk]. The monocrystal diffraction is presented in Fig. 1.

*2.3.2.2. 4β-(5-Dimethyl-1,3-dioxan-2-yl)-5β-H-cholestane (**10**).* mp: 161–164 °C; $[\alpha]_D^{25} = +17$ (c 1, $CHCl_3$); CIMS: m/z = 485 (M–H). ^{1}H NMR: δ = 0.64 (s, 3H, 18-CH_3), 0.70 (s, 3H, C$H_{3acetal}$), 0.86 (d, J = 6.6 Hz, 2× 3H, 26,27-CH_3), 0.89 (s, 3H, 21-CH_3), 0.93–1.00 and 1.80–1.85 (m, 2H, 1-CH_2), 0.94 (s, 3H, 19-CH_3), 1.03–1.13 (m, 2× 1H, 14,17-C*H*), 1.10–1.20 (m, 2H, 11-CH_2), 1.12–1.16 and 1.96–1.99 (m, 2H, 12-CH_2), 1.16 (s, 3H, C$H_{3acetal}$), 1.26–1.34 (m, 1H, 9-C*H*), 1.52–1.55 and 1.63–1.67 (m, 2H, 3-CH_2), 1.87–1.94 (m, 2H, 15-CH_2), 2.03–2.08 (m, 1H, 4-C*H*), 3.36 (d, J = 11 Hz, 2H, C$H_{2acetal}$), 3.44–3.60 (d, J = 11 Hz, 2H, C$H_{2acetal}$), 4.53 (d, J = 1.2 Hz, 1H, 4A-C*H*). ^{13}C NMR: δ = 21.8 (C$H_{3acetal}$), 22.6 (C$H_{3acetal}$), 22.8 (C-26) and (C-27), 25.0 (C-3), 35.8 (C-21), 36.1 (C-23), 37.6 (C-4), 38.4 (C-1), 39.5 (C-25), 40.1 (C-12), 46.8 (C-9), 54.5 (C-5), 56.2 (C-17), 56.5 (C-14), 77.3 (C$H_{2acetal}$), 77.4 (C$H_{2acetal}$), 102.1 (C-4A). $C_{33}H_{58}O_2$: calcd C 81.42, H 12.01, found C 81.11, H 11.96.

3. Results and discussion

3.1. Synthesis of substrates

The substrates investigated are shown in Scheme 1. Cholest-4-ene (**1**) was prepared in 74% overall yield by reduction of cholest-4-ene-3-one with $NaBH_4$ in CF_3COOH/$(CH_3CO)_2O$/CH_3CN [4]. 3-Hydroxycholest-4-ene was synthesised by reduction of cholest-4-ene-3-one with $NaBH_4$ in CH_3OH. 3β-Acetoxycholest-4-ene (**2**), 3β-acetoxypregn-5-en-20-one (**4**) and (*1R*)-(−)-myrtenyl acetate (**5**) were synthesized in 49%, 85% and 93% yield, respectively, from the corresponding alcohols by acetylation with acetic anhydride in the presence of pyridine. 3β-Acetoxycholest-5-ene (**3**) was synthesized in 90% yield from 3β-hydroxycholest-5-ene by acetylation with $(CH_3CO)_2O$ catalysed by montmorillonite [4].

3.2. Catalytic reactions

The hydroformylation catalysts were prepared *in situ* by reaction of $[Rh_2(\mu\text{-OMe})_2(cod)_2]$ with the appropriate phosphorous ligand, namely tris(*o-tert*-butylphenyl)phosphite, P(OPh*)$_3$; tris(*o*-trifluoromethylphenyl)phosphine, P(*o*-CF_3-$C_6H_4)_3$; and tris(*p*-trifluoromethylphenyl)phosphine, P(*p*-CF_3-$C_6H_4)_3$, under 40 bar of CO/H_2 (1:1) and at 100 °C. After 45 min

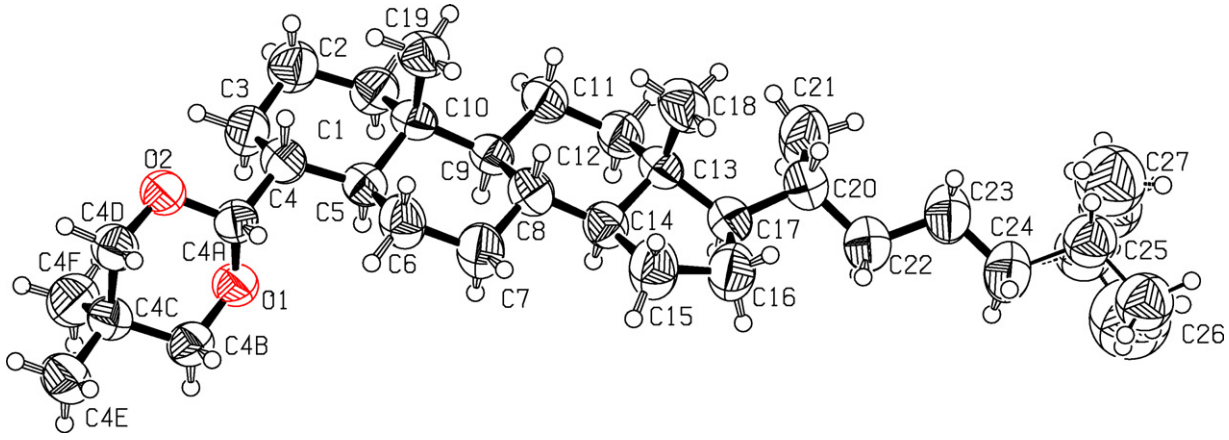
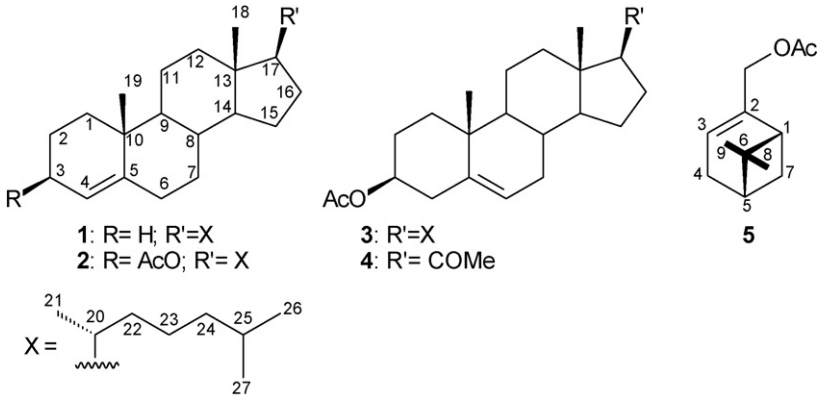


Fig. 1. Diagram of acetal **9** [31]. Displacement ellipsoids are drawn at the 50% probability level.



Scheme 1.

of incubation, the pressure was released and the substrate was introduced in the autoclave. Then, the selected reaction conditions were set. This procedure provides reproducible results, while the direct use of a mixture of the substrate with the catalytic precursor mixture did not.

Table 1 collects selected results on the hydroformylation of substrates **1**, **2**, **3** and **4**. The reaction products are shown in Scheme 2.

In the case of substrate **1**, the best results were achieved with $Rh/P(OPh^*)_3$ at 100 °C, 20 bar CO/H_2 pressure and L/Rh = 2.5 (Table 1, entry 1). This system was able to promote the hydroformylation of substrate **1** yielding two isomeric aldehydes, **6** and **7** in ratio *ca.* 30/70. Therefore, the reaction proceeds with complete regioselectivity at position 4 of the steroidal backbone, without any quaternary aldehyde formation, in good agreement with Keulemans role [22,23]. The major product **7** arises from the approach of the catalyst through the β face. This result parallels that previously observed with related substrate 17-β-acetoxyandrost-4-ene [4]. The stereochemistry of the reaction can be rationalized considering the partially folded structure of rings A and B of the steroidal backbone. In this structure the double bond is further away from the steric influence of the methyl substituent on C-10. Furthermore, the folded backbone prevents the approach of the catalyst from the α face.

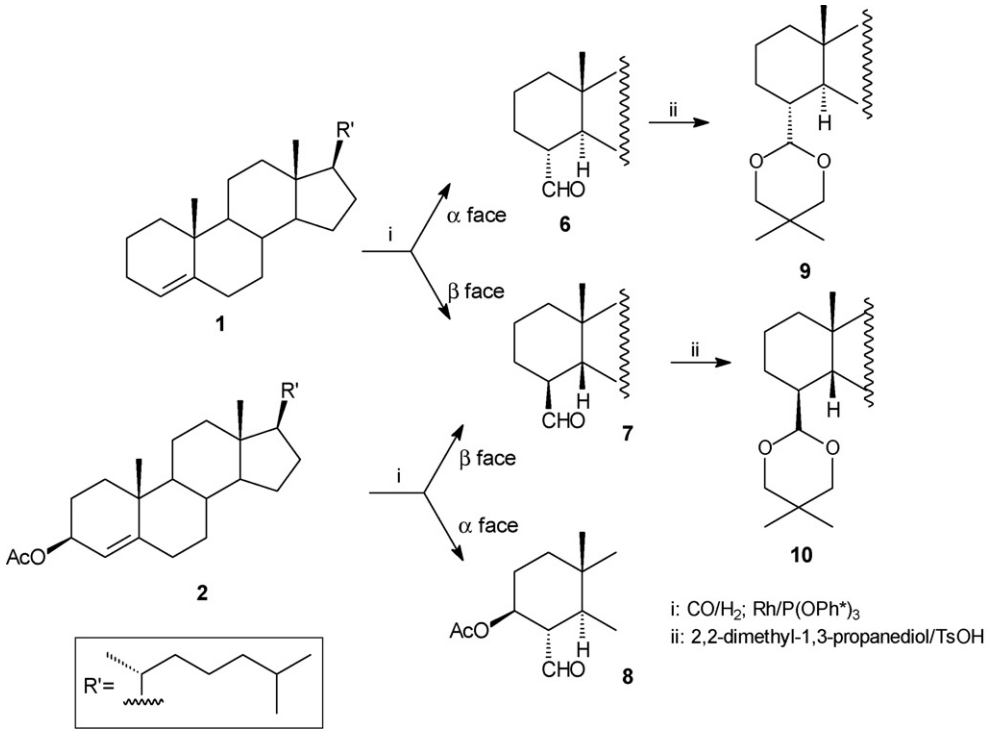
The effects of the reaction parameters on the selectivity of the catalytic reaction were investigated. Thus, an increase of pressure to 40 bar, (Table 1, entry 2), slightly increases the isomer ratio **7/6**, but the chemoselectivity decreased, mainly due to the unexpected formation of non-reactive isomeric products. Keeping the pressure at 20 bar and raising the temperature (Table 1, entries 3 and 4), the diastereoselectivity decreased. Furthermore, at 120 °C a low conversion (51%) was obtained as consequence of catalyst decomposition. At temperatures below 100 °C almost no conversion was observed.

We have also investigated the hydroformylation of substrate **1** by using Rh/trifluoromethylarylphosphine catalysts. In principle, the tris(*o*-trifluoromethylphenyl)phosphine combines both

Table 1
Hydroformylation of steroids **1**, **2**, **3** and **4** catalyzed by Rh/P-donor ligands[a]

Entry	Substrate[b]	Ligand	*T* (°C)	*P* (bar)	L/Rh	Conversion[c] (%)	Time (h)	Che.[d] (%)	Iso.[e]
1	**1**	$P(OPh^*)_3$	100	20	2.5	77	67	78	70/30[f]
2	**1**	$P(OPh^*)_3$	100	40	2.5	74	48	49	76/24[f]
3	**1**	$P(OPh^*)_3$	110	20	2.5	71	66	76	62/38[f]
4	**1**	$P(OPh^*)_3$	120	20	2.5	51	50	65	50/50[f]
5	**1**	$P(o\text{-}CF_3C_6H_4)_3$	100	20	2	<5	48	–	–
6	**1**	$P(p\text{-}CF_3C_6H_4)_3$	80	20	2	13	48	9	76/24[f]
7	**2**	$P(OPh^*)_3$	100	20	2.5	96	72	98	60/40[g]
8	**3**	$P(OPh^*)_3$	100	20	2.5	18[h]	72	–	–
9	**3**	$P(p\text{-}CF_3C_6H_4)_3$	80	20	2	<5[h]	48	–	–
10	**3**	$P(o\text{-}CF_3C_6H_4)_3$	80	20	5	<5[h]	48	–	–
11	**3**	$P(o\text{-}CF_3C_6H_4)_3$	100	100	5	<5[h]	48	–	–
12	**4**	$P(OPh^*)_3$	100	20	5	16[h]	48	–	–

[a] Reaction conditions: 2.2×10^{-2} mmol of Rh as $[Rh_2(\mu\text{-}OMe)_2(cod)_2]$ and 1.08 mmol of substrate in 6 mL toluene.
[b] Ligand to Rh molar ratio.
[c] Percentage of substrate converted.
[d] Chemoselectivity calculated as percentage of aldehydes in the total amount of converted olefin.
[e] Aldehyde ratio obtained by NMR.
[f] **7/6**.
[g] **7/8**.
[h] Only isomerised products.



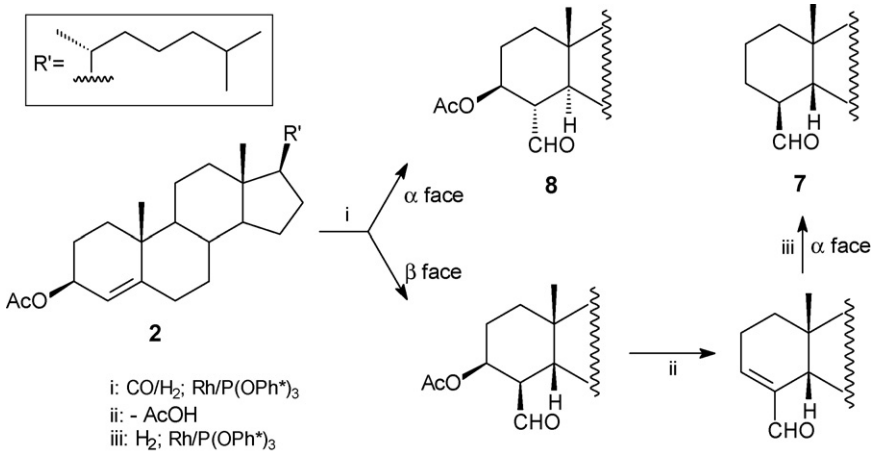
Scheme 2.

π-acidic character and a cone angle bigger than 200° [24,25], which *a priori* could mimic the properties of the bulky phosphite we have used in this study. However, the results with this ligand were disappointing, since no aldehyde formation was observed (Table 1, entry 5). The electronically comparable tris(*p*-trifluoromethylphenyl)phosphine ligand produced some conversion into aldehydes (Table 1, entry 6), but its activity is significantly worse than that achieved by the bulky phosphite. These results are consistent with the lower rates recently reported for the hydroformylation of 1-hexene with rhodium catalysts modified with fluorinated phosphines, when compared with triphenylphosphite [26]. Therefore, the bulky phosphite catalyst revealed to be considerably more active and selective than π-acid phosphines in promoting the hydroformylation of this type of steroidal substrates.

The crude reaction was purified by chromatography (silica-gel, hexane) and a mixture of aldehydes **6** and **7**, resulting from the hydroformylation of steroid **1**, was isolated in 70% yield. Using the same chromatographic conditions, the aldehyde mixture was rechromatographed and pure aldehyde **7** was isolated with 22% yield. In all the other chromatographic fractions a mixture of **6** and **7** was obtained. However, aldehyde **6** could not be isolated through this method, likely because of the poor chromatographic behaviour of aldehydes, associated by the fact of being the minor product. In order to overcome these purification problems, the mixture of the two diastereoisomeric aldehydes **6** and **7** was derivatized into the corresponding acetals using 2,2-dimethyl-1,3-propanediol and *p*-toluenesulfonic acid monohydrate as catalyst (Scheme 2). After work-up, followed by chromatographic separation and recrystallization the acetals **9** and **10** were isolated in 55% and 15% yield, respectively. The other fractions were isolated as a mixture of **9** and **10**.

The hydroformylation of acetoxy substrate **2** was studied under the optimized reaction conditions achieved for substrate **1**. Aldehyde **7** was again the major product of the hydroformylation of the acetoxy substrate **2** (Table 1, entry 7). The stereoselectivity of the reaction was very close to that of substrate **1** (Scheme 2). These results are very similar to our previous observation in the case of the 3β,17β-diacetoxyandrost-4-ene [4]. There, we proposed two possible mechanisms for this type of reaction. One would involve the formation of a η^3-allylic intermediate with abstraction of the acetoxy group [27] and the other the elimination of acetic acid after hydroformylation. In the case of substrate **2**, we have characterized in the reaction mixture the acetoxyaldehyde **8**, which strongly suggest two reactions paths, as shown in Scheme 3.

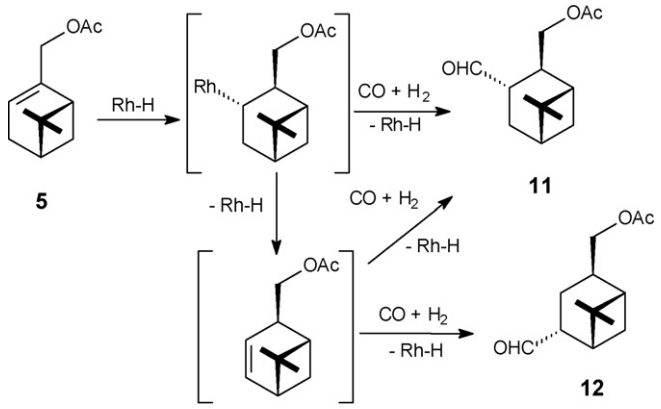
Thus, the minor product **8**, containing *trans* acetoxy and formyl groups arises from the α face hydroformylation is stable in the reaction media, while the aldehyde arising from the β face reaction contains an acidic hydrogen *trans* to the acetoxy group that readily eliminates as AcOH to form the Δ^3-4-formyl steroid. This α,β-unsaturated aldehyde is hydrogenated through the α face by the Rh catalyst, with complete stereoselectivity, yielding **7**. As expected, MS of the isotopically labelled aldehyde **7**, obtained by deuteroformylation of **2**, shows a $M+4$ molecular peak. Attempts to analyze the stereochemistry of the labeled compound, in order to corroborate the proposed mechanism, were unsuccessful. Elimination of AcOH from the products of the hydroformylation of the allylic acetates has been previously reported for glucals [28]. In the case of linear substrates, such as allylic esters, the elimination of AcOH from the branched



Scheme 3.

aldehyde is responsible for the unusually high regioselectivity observed in some cases in the hydroformylation of these substrates [29].

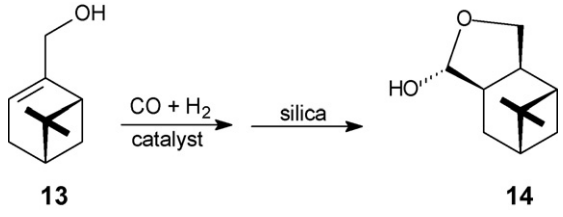
In conclusion, the presence of product **8**, which preserves the acetoxy group in the hydroformylation of substrate **2**, observed only in the ^{1}H NMR spectrum of the reaction mixture, with a typical –OCO*CH*$_3$ peak at $\delta = 2.05$ and the aldehydic proton at $\delta = 9.40$ ppm (40%), allows discarding the allylic path for the formation of the aldehyde **7** from this substrate. In order to further corroborate this hypothesis, we have investigated the hydroformylation of (1*R*)-(−)-myrtenyl acetate (**5**). The allylic acetate could in principle form an allylic intermediate, which would lead to the linear aldehyde without the acetoxy group. On the other hand, the non allylic route would produce the aldehyde **11**, Scheme 4, assuming the attack of the catalyst through the less hindered face of the double bond. This aldehyde should not eliminate AcOH. Thus, using similar reaction conditions to those used for substrate **2**, complete conversion of (1*R*)-(−)-myrtenyl acetate (**5**) was obtained after 48 h of reaction, yielding the acetoxyformyl product **11** with 71% selectivity. This demonstrates again that the allylic path does not proceed with this substrate and, therefore, neither with the steroid **2**. Furthermore, a second acetoxyformyl product **12** (28% by GC and NMR analysis) was detected in the reaction mixture (Scheme 4).



Scheme 4.

The mixture of aldehydes was fully characterized by 2D NMR spectra. The major product **11** of the hydroformylation of (1*R*)-(−)-myrtenyl acetate arise from the catalyst approach through the less hindered face of the substrate, with the expected regioselectivity for position 2, without quaternary aldehydes formation [22,23]. The minor product **12** is formed by the hydroformylation of isomerized double bond arising from β-elimination of the alkyl complex. Also for this isomerized alkene, the reaction proceeds through the face opposite to the isopropylidene bridge. It can not be discarded that at least part of the aldehyde **11** is produced from the isomerized alkene, Scheme 4, but the fact that aldehydes **11** and **12** are the only products of the reaction, indicates that both alkenes react exclusively through the face *trans* to the isopropylidene bridge. It is interesting to notice that in the hydroformylation of (1*R*)-(−)-myrtenol (**13**), Kalck et al. have observed the formation of the cyclic hemiacetal **14** arising from the hydroxylaldehyde with the formyl group *cis* to isopropylidene bridge and to the hydroxymethyl substituent (Scheme 5) [30].

In principle, this would indicate that reaction takes place through the most hindered face of the ring, contrary to our observation, and also an unusual *trans* addition of the H and CHO group to the double bond. Kalck et al. suggested that the stereochemistry could be explained by racemization of the aldehyde through the enol formation during the chromatographic manipulation or to a kinetic control of the hydroformylation process leading to the most unstable aldehyde. From our results, it seems clear that both substrates, **5** and **13**, form the aldehyde with the formyl group *trans* to the isopropylidene bridge, with the expected *cis* addition of the formyl group and hydro-



Scheme 5.

gen atom. Then, in the case of the (1*R*)-(−)-myrtenol an epimerization equilibrium shifted to the *trans* isopropylidene isomer by the formation of the hemiacetal is the most plausible explanation.

All attempts to perform the hydroformylation of the 3β-acetoxy-Δ^5-steroids, **3** and **4**, were unsuccessful, regardless of the co-catalyst and the reaction conditions used (Table 1, entries 8–12 show some characteristic results). For all these reactions, only small amounts of isomerised olefinic products have been obtained, along with the unreacted starting materials, as confirmed by GC/MS with the presence of two mass peaks at 428 and 358, respectively. The hydroformylation reaction probably failed due to major steric hindrance between the Δ^5 double bond in the B-ring and the catalyst, when compared to that of the Δ^4 double bond, as was recently proposed by Kollár.[5].

3.3. Characterization of products

The hydroformylation reaction of substrate **1** gave two products, 4α-formyl-5α-*H*-cholestane (**6**) and 4β-formyl-5β-*H*-cholestane (**7**), being the last the major product (Scheme 2), identified by GC–MS by the presence of mass peaks at 401 $(M+H)^+$ and by ^{1}H NMR spectrum by typical aldehydic protons at δ 9.41 and 9.43 ppm.

The analysis of the ^{1}H and ^{13}C NMR spectra of the isolated aldehyde 4β-formyl-5β-*H*-cholestane (**7**), assisted by 2D NMR experiments (COSY, HSQC, HMBC and NOESY spectra), allows the assignment of most of their proton and carbon resonances and also of the stereochemistry of the product. The assignments of the majority of ^{1}H and ^{13}C resonances are presented in Section 2.3.1.

The isolated 4α-(5-dimethyl-1,3-dioxan-2-yl)-5-α-*H*-cholestane (**9**) and 4β-(5-dimethyl-1,3-dioxan-2-yl)-5-β-*H*-cholestane (**10**), were also fully characterized by 2D NMR spectra and allows the assignments of their proton and carbon resonances described in Section 2.3.2. The 4α-(5-dimethyl-1,3-dioxan-2-yl)-5-α-*H*-cholestane (**9**) was also characterized by X-ray structural analysis.

The molecular structure of acetal **9**, obtained through X-ray analysis of the monocrystal diffraction is shown in Fig. 1 [21,31]. The structure shows that rings A, B and C are all trans-fused with normal slightly flattened chair conformations, typical of a 5α-epimer. The substituent C-4A atom is bonded to C-4 in an equatorial position. The C(4A)–C(4)–C(5) and C(4)–C(5)–C(6) angles are 113.5(2)° and 113.8(2)°, respectively. The 5-membered ring adopts a conformation close to half-chair with C-20 bonding to C-17 in an equatorial position. The molecule has fully extended, all-*trans* side chain, with the terminal atoms disordered over two positions with roughly 50% occupation each. The six-membered ring C(4A)–O1–C(4B)–C(4C)–C(4D)–O2 adopts a slightly distorted chair conformation. The least-squares plane of this ring makes an angle of 63° with the least squares plane of all the carbon atoms of rings A, B, C and D.

Table 2
^{13}C and ^{1}H NMR data for aldehydes **11** and **12**

	11		**12**	
	^{13}C	^{1}H	^{13}C	^{1}H
C1	40.3	2.02–2.08	38.6	1.98–2.00
C2	39.8	2.65–2.70	42.5	2.37–2.41
C3	44.4	2.65–2.70	17.2	1.45–1.52 and 2.51–2.59
C4	26.6	2.14–2.16	49.4	2.90–2.94
C5	42.2	2.02–2.08	41.0	2.37–2.41
C7	32.0	0.75 (d, J = 10.2 Hz), 1.99–2.04	28.6	0.87–0.89 and 2.25–2.32
CH_3-8	23.0	1.23	28.3	1.25
CH_3-9	27.3	1.01	23.1	1.06
CHO	202.2	9.64 (d, J = 1.1 Hz)	203.6	9.66
CO_2CH_3	171.1	–	171.1	–
CO_2CH_3	20.9	2.04	21.0	2.05
CH_2O	67.8	4.08–4.16	68.4	4.06 (d, J = 7.8 Hz)

The assignments obtained are in accordance with the assignments obtained by Lee [19] for the carbons C1, C5, C6, C7, C8 and C9 and respective protons.

It was not possible to separate aldehydes **11** and **12** arising from the hydroformylation of (1*R*)-(−)-myrtenyl acetate **5**. Their characterization was carried out by GC–MS and ^{1}H and ^{13}C NMR spectra of the mixture, assisted by 2D NMR experiments (COSY, HMBC, HSQC, DEPT-135 and NOESY) allowing the assignments of most of their proton and carbon resonances, shown in Table 2, and also the stereochemistry of the products.

The main connectivities found in HMBC and HSQC spectra were important to determine de regioselectivity of the products. Therefore for the aldehyde **11** there is evidence of correlation of the aldehydic signal C*H*O with that of C-3 (δ = 44.4) and

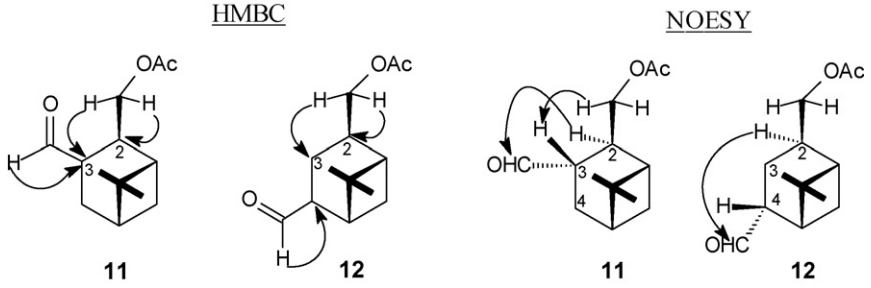


Fig. 2. Main connectivities found in the HMBC and NOE cross peaks observed in the NOESY spectra of **11** and **12**.

also with the protons CH_2OAc and the carbons C-2 ($\delta = 39.8$) and C-3 ($\delta = 44.4$) (Fig. 2). On the other hand aldehyde **12** shows correlations of the formyl signal C*H*O with that of C-4 ($\delta = 49.4$) and one of the proton CH_2OAc with the carbons C-3 ($\delta = 17.2$) and C-2 ($\delta = 42.5$). With these observations it was possible to determine the regioselectivity of **11** with the formyl group in position 3 and aldehyde **12** with C*H*O in position 4, Fig. 2.

The intense NOE cross peaks observed in NOESY spectrum were important to determine the stereochemistry of the two aldehydes, 3-formyl and 4-formyl myrtenyl acetate **11** and **12** (Fig. 2). For aldehyde **11** intense NOE cross peaks were observed between C*H*O group and H-2 indicating close proximity. NOE cross peaks were also observed with CH_2OAc, H-3 and CH_3-8 (methylenic bridge) indicating that they are on the same β-face. These observations were important to conclude that the formyl group was bonded to the less hindered α-face, *trans* to the methyl acetoxy group. For aldehyde **12** similar interactions were observed. There is also evidence of intense NOE cross peaks between C*H*O and the H-2, being the methylenic bridge and the CH_2OAc on the same β-face, and as it would be expected the aldehyde is bonded to the less hindered α-face (Fig. 2).

4. Conclusion

This paper shows that catalytic hydroformylation using Rh-tris(*o-tert*-butylphenyl)phosphite is a useful synthetic strategy to produce 4-formyl derivatives from the Δ^4-steroids, with 60–70% β-diastereoselectivity, yielding the 4β-formyl-5β-*H*-cholestane (**7**). The derivatization of these new formyl steroids **6** and **7** to the corresponding acetals **9** and **10**, allows an easier purification and full characterization by 2D NMR and X-ray analysis of 4α-(5-dimethyl-1,3-dioxan-2-yl)-5α-*H*-cholestane (**9**). None of catalysts assayed were effective to promote the hydroformylation of Δ^5-steroids.

Finally, it has been shown that one of the *cis* acetoxyformyl stereoisomers of the Δ^4-3β-acetoxy undergoes sequential AcOH elimination and subsequent hydrogenation to yield the 4-formyl derivative. As expected, the *trans* acetoxy stereoisomer is stable under the reaction conditions. This mechanism was corroborated by the products obtained from the hydroformylation of (1*R*)-(−)-myrtenyl acetate where no AcOH elimination was observed, demonstrating that the allylic path is not involved. From these observations we have strong evidence that the hydroformylation reactions of acetoxy steroids do not take place through an allylic intermediate, but undergo AcOH elimination followed by stereoselective hydrogenation of α,β-unsaturated aldehyde.

Our results also demonstrate that the hydroformylation reaction of (1*R*)-(−)-myrtenyl acetate proceeds with 100% diastereoselectivity, through the face opposite to the isopropylidene brigde.

Acknowledgements

The authors thank Portuguese FCT, POCTI and Spanish DGI (project CTQ2005-09187-C02-01) for financial support and CYTED (Project V.9). A. Peixoto would like to thank to FCT the PhD grant (SFRH/BD/29681/2006).

References

[1] E. Flores, E. Bratoeff, M. Cabeza, E. Ramirez, A. Quiroz, I. Heuze, Mini Rev. Med. Chem. 3 (2003) 225.
[2] A.M.H. Brodie, V.C.O. Njar, Steroids 65 (2000) 171.
[3] J. Mann, B. Pietrzak, Tetrahedron 45 (1989) 1549.
[4] Z. Freixa, M.M. Pereira, J.C. Bayón, A.M.S. Silva, J.A.R. Salvador, A.M. Beja, J.A. Paixão, M. Ramos, Tetrahedron: Assymm. 12 (2001) 1083.
[5] R. Skoda-Földes, L. Kollár, Chem. Rev. 103 (2003) 4095.
[6] M. Haase-Held, M. Hatzis, J. Mann, J. Chem. Soc., Perkin Trans. 1 (1993) 2907.
[7] E. Fernández, S. Castillón, in: P.W.N.M. van Leeuwen, C. Claver (Eds.), Rhodium Catalyzed Hydroformylation, Kluwer Academic, Dordrecht, 2000, pp. 145–182.
[8] C. Botteghi, M. Marchetti, S. Paganelli, in: M. Beller, C. Bolm (Eds.), Transition Metal for Organic Synthesis, Wiley–VCH, 1998, pp. 23–48.
[9] B. Breit, W. Seiche, Synthesis (2001) 1.
[10] A. Peixoto, M.M. Pereira, M.G.P.M.S. Neves, A.M.S. Silva, J.A.S. Cavaleiro, Tetrahedron Lett. 44 (2003) 5593.
[11] P.F. Beal, M.A. Rebenstorf, J.E. Pike, J. Am. Chem. Soc. 81 (1959) 1231.
[12] S. Toros, I. Gémes-Pécsi, B. Heil, S. Mahó, Z. Tuba, J. Chem. Soc., Chem. Commun. (1992) 858.
[13] S. Toros, B. Heil, G. Gálik, Z. Tuba, Tetrahedron Lett. 33 (1992) 3667.
[14] E. Nagy, B. Heil, S. Toros, J. Mol. Catal. A: Chem. 143 (1999) 229.
[15] R. Usón, L.A. Oro, J. Cabeza, J. Inorg. Synth. 23 (1985) 126.
[16] P.W.N.M. van Leeuwen, C.F. Roobeek, J. Organomet. Chem. 258 (1983) 343.
[17] Dictionary of Organic Compounds, vol. 2, Eyre and Spottiswoode Publishers Ltd., London, 1936, pp. 700–701.
[18] W. Neudert, H. Röpke, Atlas of Steroid Spectra, Springer-Verlag, Berlin, 1965.
[19] S.-G. Lee, Magn. Reson. Chem. 40 (2002) 311.
[20] G.M. Sheldrick, SHELXS97 and SHELXL97, University of Gottingen, Germany, 1997.
[21] Crystal data deposited at the Cambridge Crystallographic Data Center.
[22] A.I.M. Keulemans, A. Kwantes, T. Vanbavel, Recl. Trav. Chim. Pays-Bas 67 (1948) 298.
[23] M.L. Clarke, Curr. Org. Chem. 9 (2005) 701.
[24] P. Soumalainen, H.K. Reinius, H. Riihimäki, R.H. Laitinen, S. Jääskeläinen, M. Haukka, J.T. Pursiainen, T.A. Pakkanen, A.O.I. Krause, J. Mol. Catal. A: Chem. 169 (2001) 67.
[25] R.T. Boeré, Y. Zhang, J. Organomet. Chem. 690 (2005) 2651.
[26] M.L. Clarke, D. Ellis, K.L. Mason, A.G. Orpen, P.G. Pringle, R.L. Wingad, D.A. Zaher, R.T. Baker, Dalton Trans. (2005) 1294.
[27] C.M. Foca, H.J.V. Barros, E.N. dos Santos, E.V. Gusevskaya, J.C. Bayón, New J. Chem. 27 (2003) 533 (and references therein).
[28] E. Fernández, A. Polo, A. Ruiz, C. Claver, S. Castillón, Chem. Commun. (1998) 2003.
[29] H. Alper, J.Q. Zhou, J. Chem. Soc., Chem. Commun. (1993) 316.
[30] S. Sirol, J.-P. Gorrichon, P. Kalck, P.M. Nieto, G. Gommenges, Magn. Reson. Chem. 37 (1999) 127.
[31] ORTEP: C.K. Johnson, ORTEPII, Report ORNL-5138, Oak Ridge National Laboratory Tennessee, USA, 1976.