Steroids 78 (2013) 1092–1097

Contents lists available at ScienceDirect

Steroids

journal homepage: www.elsevier.com/locate/steroids

Synthesis of 24-phenyl-24-oxo steroids derived from bile acids by palladium-catalyzed cross coupling with phenylboronic acid. NMR characterization and X-ray structures

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ARTICLE INFO

Article history:
Received 28 May 2013
Received in revised form 3 July 2013
Accepted 24 July 2013
Available online 2 August 2013

Keywords:
Bile acids
Phenylboronic acid
Palladium-catalyzed cross coupling
24-Phenyl-24-oxo steroids

ABSTRACT

Palladium-catalyzed cross coupling of phenyboronic acid with acetylated bile acids in which the carboxyl functions have been activated by formation of a mixed anhydride with pivalic anhydride afforded moderate to good yield of 24-phenyl-24-oxo-steroids. Unambiguous assignments of the NMR signals were made with the aid of combined 1D and 2D NMR techniques. X-ray diffraction studies confirmed the obtained structures.

1. Introduction

The preparation of ketones is probably one of the most widespread transformations in organic synthesis. In particular the synthesis of phenyl ketones is involved the preparation of a wide variety of bioactive compounds [1]. Although the preparation of phenyl ketones can be, in general, achieved by the classical Friedel Crafts acylation [2] the incompatibility of several functional groups with the harsh reaction conditions that predominate in Friedel Craft acylation has prompted the development of alternative methods mainly based on the reaction of acyl chlorides with organometallic reagents [3].

The preparation of phenyl ketones derived from steroidal carboxylic acid has received limited attention, and to the best of our knowledge it has been only achieved by treatment of the corresponding acyl chloride with diphenylcadmium. Thus, treatment of the 3β-acetate of the acyl chloride **2** with diphenylcadmiun afforded the corresponding phenyl ketone in good yields [4]. Similar treatment of the acyl chorides (like **4**) derived from formylated bile and nor-bile acids produced good yields of the corresponding ketones [5]. The fact all these transformations involve the preparation and manipulation of acyl chlorides of low stability and limited tolerance to several functional groups is a considerable disadvantage of this methodology. An additional drawback of this methodology is that preparation of diphenylcadmiun implies the usage of highly toxic cadmium salts (i.e. $CdCl_2$), as well as the moisture-sensitive phenylmagnesium bromide which low functional group tolerance also limits the scope of this methodology. (see Scheme. 1)

Palladium catalyzed cross couplings of carboxylic anhydrides with arylboronic acids have emerged as a convenient alternative for the preparation of arylketones [6]. The fact that the starting carboxylic anhydride can be generated *in situ* allowed the design of attractive one-pot procedures for the preparation of phenylketones in high to good yields [7]. In addition, the high stability and wide functional group tolerance of arylboronic acid make this cross coupling a versatile synthetic alternative for the synthesis of aryl ketones.

After those facts and in connection with our program on the synthesis of potentially bioactive steroids we decided to setup adequate conditions for the preparation of a collection of phenyl ketones derived from several bile acids. Herein we report on the synthesis of 24-phenyl-24-oxo steroids by palladium-catalyzed cross coupling of bile acids and phenylboronic acid.

During the course of this research, we became aware that no NMR data is available for this kind of compound. Hence we decided to carry out the unambiguous assignments of the NMR signals of the obtained compounds. Additionally, the crystal structures of two of the obtained steroidal phenyl ketones are provided.

2. Experimental

The starting acetylated bile acids **5**–**9** were prepared following the standard Ac_2O/pyr/DMAP procedure. Reactions were

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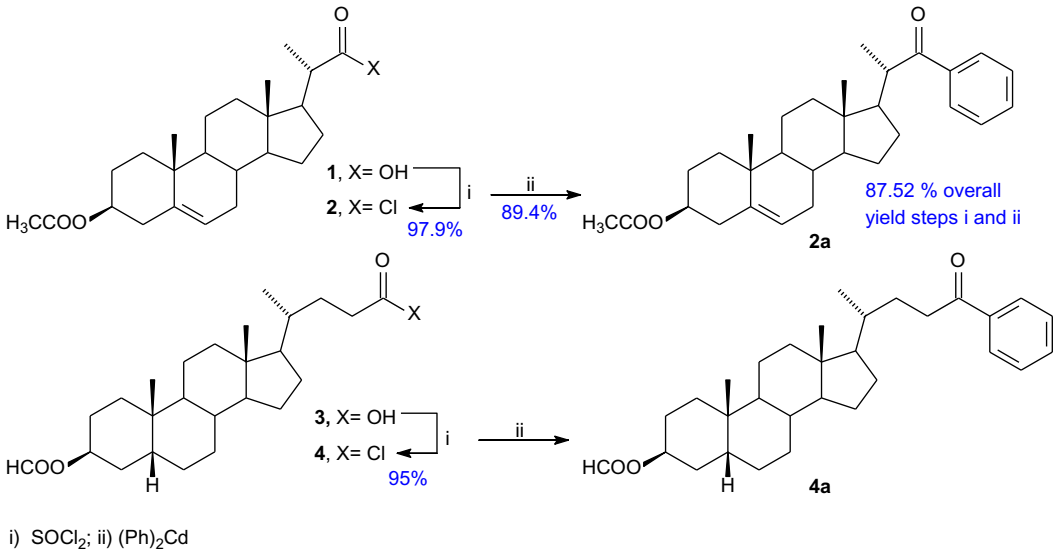
http://dx.doi.org/10.1016/j.steroids.2013.07.008



Scheme 1. Synthesis of phenyl ketones derived from steroidal acyl chlorides.

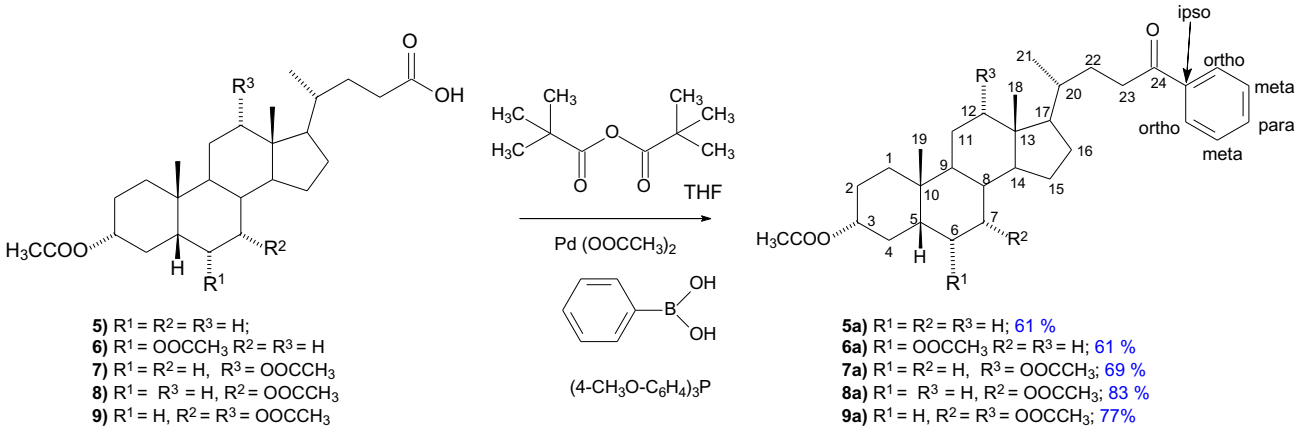
monitored by TLC on ALUGRAM® SIL G/UV254 plates from MACHEREY-NAGEL. Chromatographic plates were sprayed with a 1% solution of vanillin in 50% $HClO_4$ and heated until color developed. Melting points were measured on a Melt-Temp II apparatus. Mass spectra were registered in a thermo-electron spectrometer model DFS (Double Focus Sector). NMR spectra were recorded in $CDCl_3$ solution in a Varian INOVA 400 spectrometer using the solvent signal 7.26 ppm for ^1H and 77.00 ppm for ^{13}C as references. (For copies of the ^1H and ^{13}C NMR spectra see supporting information file) NMR signals assignments in the starting materials **5**–**9** and the obtained ketones **5a**–**9a** were carried out with the aid of a combination of 1D and 2D NMR techniques that included ^1H, ^{13}C, (^1H–^1H), ^1H–^1H COSY, Nuclear Overhauser Effect Spectroscopy (NOESY), Heteronuclear Single Quantum Correlation (HSQC) and Heteronuclear Multiple Bond Correlation (HMBC). All 2D NMR spectra were recorded using the standard pulse sequences and parameters recommended by the manufacturer and processed and were processed employing the MestreNova NMR processing program [See http://mestrelab.com/].

2.1. General procedure for cross coupling

$Pd(CH_3COO)_2$ (10.05 mg, 0.045 mmol), the acetylated bile acid (1.00 mmol), pivalic anhydride (418.25 mg, 2.25 mmol dissolved in 4 mL of THF); H_2O (0.067 mL, 67.5 mg, 3.75 mmol); phenylboronic acid (219 mg, 1.8 mmol dissolved in 2 mL of THF) and tris(p-metoxyphenyl)phosphine (37.05 mg, 0.105 mmol) were added in this order to a flask under sonication and the atmosphere

Table 1
Crystal data and structure refinement for compounds **7a** and **8a**.

Parameters	7a	8a
Empirical formula	$C_{34}H_{48}O_5$	$C_{34}H_{48}O_5$
Formula weight	536.72	536.72
Temperature	130 (2) K	293 (2) K
Wavelength	0.71073 Å	0.71073 Å
Crystal system	Monoclinic	Orthorhombic
Space group	P 21	P 21 21 21
Unit cell dimensions	a = 13.8480 (13) Å	a = 6.3077 (4) Å
	b = 8.1490 (6) Å	b = 21.1380 (14) Å
	c = 14.3790 (12) Å	c = 23.170 (2) Å
	β = 114.422 (11)°	
Volume	1477.4 (2) Å^3	3089.3 (4) Å^3
Z	2	4
Density (calculated)	1.206 Mg/m^3	1.154 Mg/m^3
Absorption coefficient	0.079 mm^{-1}	0.076 mm^{-1}
F(000)	584	1168
Crystal size	0.593 × 0.4009 × 0.1836 mm^3	0.5224 × 0.5164 × 0.4351 mm^3
Theta range for data collection	3.44–26.06°	3.52–26.73°
Index ranges	$-13 \leqslant h \leqslant 17$, $-10 \leqslant k \leqslant 9$, $-17 \leqslant l \leqslant 17$	$-7 \leqslant h \leqslant 6$, $-26 \leqslant k \leqslant 23$, $-29 \leqslant l \leqslant 26$
Reflections collected	10839	9724
Independent reflections	5412 [R(int) = 0.0494]	6190 [R(int) = 0.0351]
Completeness to theta = 26.06°	99.6 %	99.3 %
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data /restraints/parameters	5412/1/357	6190/0/357
Goodness-of-fit on F2	1.041	1.011
Final R indices [I > 2sigma(I)]	R1 = 0.0527, wR2 = 0.0846	R1 = 0.0558, wR2 = 0.0961
R indices (all data)	R1 = 0.0986, wR2 = 0.1035	R1 = 0.1198, wR2 = 0.1197
Largest diff. peak and hole	0.190 and −0.199 e.Å^{-3}	0.184 and −0.154 e.Å^{-3}



5) $R^1 = R^2 = R^3 = H$;
6) $R^1 = OOCCH_3$ $R^2 = R^3 = H$
7) $R^1 = R^2 = H$, $R^3 = OOCCH_3$
8) $R^1 = R^3 = H$, $R^2 = OOCCH_3$
9) $R^1 = H$, $R^2 = R^3 = OOCCH_3$

5a) $R^1 = R^2 = R^3 = H$; 61 %
6a) $R^1 = OOCCH_3$ $R^2 = R^3 = H$; 61 %
7a) $R^1 = R^2 = H$, $R^3 = OOCCH_3$; 69 %
8a) $R^1 = R^3 = H$, $R^2 = OOCCH_3$; 83 %
9a) $R^1 = H$, $R^2 = R^3 = OOCCH_3$; 77%

Scheme 2. Synthesis of 24-oxo-24-phenyl steroids.

was purged with Ar twice. The reaction mixture was stirred under Ar at 60 °C until TLC indicated consumption of the starting material and the solvent was evaporated. In each case the produced dark solids were applied to a chromatographic column that was eluted with hexane/ethyl acetate mixtures to afford the desired phenyl ketone.

3α-Acetoxy-24-phenyl-5β-cholan-24-one **(5a)**. Yied 61%, Reaction time 48 h. Mp 171.5–172.7 °C *(from AcOEt/CH_2Cl_2)*. **^{1}H NMR (400 MHz, $CDCl_3$)** δ(ppm) 8.02-7.87 (2H, m, H-ortho), 7.57-7.52 (1H, m, H-para), 7.48–7.43 (2H, m, H-meta), 4.71 (1H, tt, *J* = 11.4, 4.8 Hz, H-3β), 2.99 (1H, ddd, *J* = 16.3, 10.2, 5.0 Hz, H-23a), 2.88 (1H, ddd, *J* = 15.9, 9.6, 5.9 Hz, H-23b), 2.02 (3H, s, CH_3 acetyl), 0.98 (3H, d, *J* = 6.3 Hz, H-21), 0.92 (3H, s, H-19), 0.65 (3H, s, H-18). **^{13}C NMR (100 MHz, $CDCl_3$)** δ(ppm) 35.0 C-1, 26.3 C-2, 74.4 C-3, 32.2 C-4, 41.9 C-5, 27.0 C-6, 26.6 C-7, 35.8 C-8, 40.4 C-9, 34.6 C-10, 20.8 C-11, 40.2 C-12, 42.7 C-13, 56.5 C-14, 24.2 C-15, 28.2 C-16, 56.1 C-17, 12.0 C-18, 23.3 C-19, 35.5 C-20, 18.6 C-21, 30.5 C-22, 35.5 C-23, 201.0 C-24, 21.4 CH_3 acetyl, 170.6 C=O acetyl, 137.1 ipso, 132.8 para, 128.5 meta, 128.0 orto. MS (70 e^-V) 478 M^+ (0.23), 315 (28), 299 (13), 298 (14), 257 (20), 255 (19), 216 (11), 215 (29), 161 (14), 147 (16), 135 (12), 133 (25), 121 (25), 120 (86), 119 (12), 109 (13), 108 (11), 107 (25), 95 (23), 93 (28), 91 (16), 81 (26), 79 (18), 77 (25), 67 (15), 55 (14).

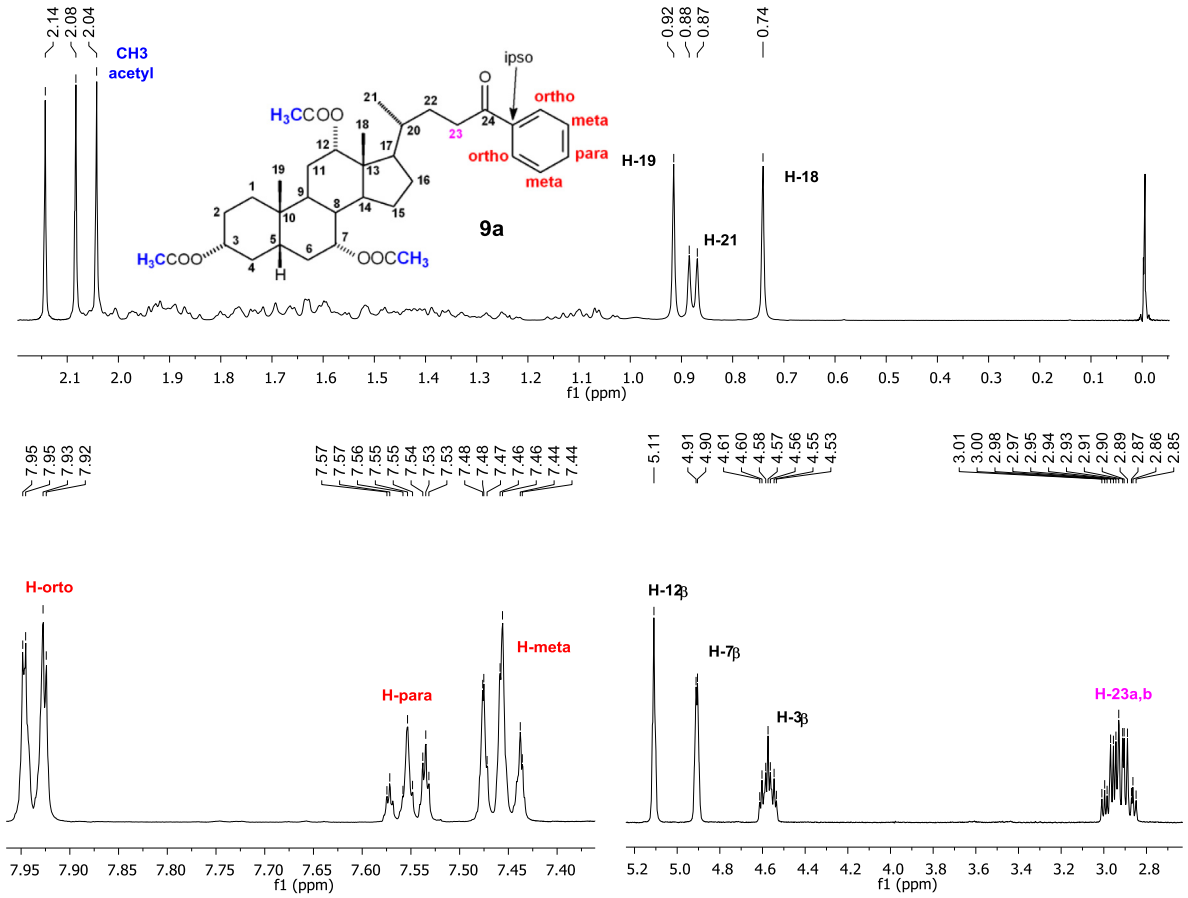


Fig. 1. H1 NMR spectra of compound **9a.**

Table 2
^{13}C NMR signals and shielding effects in the side chain of the obtained ketones.

	C-17	C-18	C-20	C-21	C-22	C-23	C-24	ipso	ortho	meta	para
5	56.0	12.1	35.3	18.2	30.7	31.0	180.4	–	–	–	–
5a	56.1	12.0	35.5	18.6	30.5	35.5	201.0	137.1	128.0	128.5	132.8
Δ ppm	+0.1	−0.1	+0.2	+0.4	−0.2	+4.5	+20.6	–	–	–	–
6	55.9	12.0	35.2	18.3	30.7	31.0	179.9	–	–	–	–
6a	56.1	12.0	35.5	18.6	30.4	35.5	200.9	137.1	128.0	128.5	132.8
Δ ppm	+0.2	0	+0.3	+0.3	−0.3	+4.5	+21.0	–	–	–	–
7	47.5	12.4	34.6	17.4	30.6	30.9	180.0	–	–	–	–
7a	47.9	12.4	35.0	17.9	30.3	35.6	200.8	137.1	128.0	128.6	132.9
Δ ppm	+0.4	0	+0.4	+0.5	−0.3	+4.7	+20.8	–	–	–	–
8	55.7	11.7	35.2	18.2	30.7	30.9	179.9	–	–	–	–
8a	55.9	11.7	35.5	18.6	30.4	35.5	200.9	137.1	128.0	128.5	132.8
Δ ppm	+0.2	0	+0.3	+0.4	-0.3	+4.6	+21.0	–	–	–	–
9	47.3	12.3	34.5	17.5	30.5	30.8	179.4	–	–	–	–
9a	47.7	12.3	34.9	17.9	30.3	35.6	200.8	137.0	128.0	128.6	132.9
Δ ppm	+0.4	0	+0.4	+0.4	−0.2	+4.8	+21.4	–	–	–	–
A	+0.26	−0.02	+0.32	+0.4	−0.26	+4.62	+20.96	–	–	–	–

$$\mathrm{A(average)} = \frac{\sum \Delta \mathrm{ppm}}{5}$$

3α,6α-Diacetoxy-24-phenyl-5β-cholan-24-one **(6a)**. Yield 61%, Reaction time 24 h. Mp. 120.6–122.2 °C (*from CH_2Cl_2*). **^{1}H NMR (400 MHz, $CDCl_3$)** δ(ppm) 7.97-7.92 (m, 2H, H-ortho), 7.55 (t, *J* = 7.3 Hz, 1H, H-para), 7.45 (t, *J* = 7.5 Hz, 2H, H-meta), 5.14 (dt, *J* = 12.1, 4.7 Hz, 1H, H-6β), 4.70 (ddd, *J* = 15.9, 11.0, 4.6 Hz, 1H, H-3β), 2.98 (ddd, *J* = 15.2, 10.0, 5.0 Hz, 1H, H-23a), 2.93-2.84 (m, 1H, H-23b), 2.03 (s, 3H, CH_3 acetyl), 2.01 (s, 3H, CH_3 acetyl), 0.97 (d, *J* = 5.7 Hz, 3H, H-21), 0.97 (s, 3H, H-19), 0.65 (s, 3H, H-19). **^{13}C NMR (100 MHz, $CDCl_3$)** δ(ppm) 35.0 C-1, 26.4 C-2, 73.7 C-3, 26.2 C-4, 45.3 C-5, 70.9 C-6, 31.3 C-7, 34.6 C-8, 39.9 C-9, 36.0 C-10, 20.7 C-11, 39.9 C-12, 42.9 C-13, 56.2 C-14, 24.1 C-15, 28.2 C-16, 56.1 C-17, 12.0 C-18, 23.2 C-19, 35.5 C-20, 18.6 C-21, 30.4 C-22, 35.5 C-23, 200.9 C-24, 21.4, 21.4 CH_3 acetyl, 170.5, 170.5 C═O acetyl, 137.1 ipso, 132.8 para, 128.5 meta, 128.0 ortho. MS (70 e$^-$V) 373 (14), 297 (29), 296 (26), 255 (28), 253 (13), 228 (10), 213 (22), 173 (10), 161 (13), 159 (19), 147 (11), 145 (19), 133 (25), 131 (11), 121 (18), 120 (80), 119 (10), 107 (15), 105 (100), 95 (15), 93 (14), 81 (15), 77 (16).

3α,12α-Diacetoxy-24-phenyl-5β-cholan-24-one **(7a)**. Yield 69%, Reaction time 26 h. Mp. 136.1–137.3 °C (*from benzene*). **^{1}H NMR (400 MHz, $CDCl_3$)** δ(ppm) 7.94 (ddd, *J* = 8.5, 2.2, 1.2 Hz, 2H, H-ortho), 7.57-7.52 (m,1H H-para), 7.48-7.42 (m, 2H, H-meta), 5.12-5.07 (m, 1H, H-12β), 4.69 (ddd, *J* = 15.9, 11.2, 4.6 Hz, 1H, H-3β), 2.97 (ddd, *J* = 14.9, 9.9, 4.9 Hz, 1H, H-23a), 2.92 – 2.80 (m, 1H, H-23b), 2.10 (s, 3H, CH_3 acetyl in 12), 2.02 (s, 3H CH_3 acetyl in 3), 0.90 (s, 3H, H-19), 0.87 (d, *J* = 6.3 Hz, 3H, H-21), 0.73 (s, 3H, H-18). **^{13}C NMR (100 MHz, $CDCl_3$)** δ(ppm) 34.7 C-1, 26.6 C-2, 74.2 C-3, 32.3 C-4, 41.8 C-5, 27.4 C-6, 25.9 C-7, 35.6 C-8, 34.4 C-9, 34.0 C-10, 26.9 C-11, 75.9 C-12, 45.1 C-13, 49.4 C-14, 23.5 C-15, 25.6 C-16, 47.9 C-17, 12.4 C-18, 23.1 C-19, 35.0 C-20, 17.9 C-21, 30.3 C-22, 35.6 C-23, 200.8 C-24, 21.4, 21.4 CH_3 acetyl, 170.5, 170.5 C═O acetyl, 137.1 ipso, 132.9 para, 128.6 meta, 128.0 ortho. MS (70 e$^-$V) 416 (11), 356 (14), 315 (11), 298 (15), 297 (68), 296 (26), 283 (15), 256 (17), 255 (76), 253 (19), 213 (12), 201 (11), 187 (15), 173 (12), 161 (29), 160 (11), 159 (16), 147 (25), 145 (21), 135 (13), 134 (18), 133 (24), 131 (14), 121 (17), 120 (30), 119 (17), 109 (12), 107 (22), 106 (11), 105 (100), 95 (17), 93 (20), 91 (18), 81 (19), 79 (14), 77 (21), 67 (12), 55 (12).

3α,7α-Diacetoxy-24-phenyl-5β-cholan-24-one **(8a)**. Yield 83%, Reaction time 45 h. Mp. 153.7–154.9 °C (*from CH_2Cl_2*). **^{1}H NMR (400 MHz, $CDCl_3$)** δ(ppm) 7.97-7.93 (m, 2H, H-ortho), 7.54 (ddd, *J* = 6.7, 3.9, 1.3 Hz, 1H, H-para), 7.48-7.42 (m, 2H, H-meta), 4.87 (m, 1H, H-7β), 4.58 (tt, *J* = 11.4, 4.4 Hz, 1H, H-3β), 3.03-2.83 (m, 2H, H-23), 2.04 (s, 3H, CH_3 acetyl), 2.02 (s, 3H, CH_3 acetyl), 0.98 (d, *J* = 6.3 Hz, 3H, H-21), 0.93 (s, 3H, H-19), 0.66 (s, 3H, H-18). **^{13}C NMR (100 MHz, $CDCl_3$)** δ(ppm) 34.6 C-1, 26.8 C-2, 74.1 C-3, 34.9 C-4, 40.9 C-5, 31.3 C-6, 71.2 C-7, 37.9 C-8, 34.1 C-9, 34.8 C-10, 20.6 C-11, 39.5 C-12, 42.7 C-13, 50.4 C-14, 23.6 C-15, 28.1 C-16, 55.9 C-17, 11.7 C-18, 22.7 C-19, 35.5 C-20, 18.6 C-21, 30.4 C-22, 35.5 C-23, 200.9 C-24, 21.4, 21.6 CH3 acetyl, 170.4, 170.6 C═O acetyl, 137.1 ipso, 132.8 para, 128.5 meta, 128.0 ortho. MS (70 e$^-$V) 416 (25), 401 (23), 313 (10), 297 (24), 296 (20), 281 (11), 256 (11), 255 (53), 253 (25), 228 (14), 213 (30), 201 (20), 199 (11), 187 (11), 185 (12), 173 (13), 171 (14), 161 (19), 159 (21), 157 (12), 147 (16), 145 (24), 143 (11), 135 (11), 134 (10), 133 (28), 131 (18), 121 (15), 120 (36), 119 (18), 117 (11), 107 (17), 106 (13), 105 (100), 95 (16), 93 (19), 91 (23), 81 (18), 79 (18), 77 (26), 67 (12), 55 (15).

3α,7α,12α-Triacetoxy-24-phenyl-5β-cholan-24-one **(9a)**. Yield 77%, Reaction time 45 h. Mp. 106.2–108.4 °C *(from acetone)*. **^{1}H NMR (400 MHz, $CDCl_3$)** δ(ppm) 7.94 (dd, *J* = 8.4, 1.3 Hz, 2H, H-ortho), 7.58-7.53 (m, 1H, H-para), 7.49-7.42 (m, 2H, H-meta), 5.11 (m, 1H, H-12β), 4.91 (m, 1H, H-7β), 4.57 (ddd, *J* = 15.6, 11.3, 4.3 Hz, 1H H-3β), 3.02-2.84 (m, 2H, H-23), 2.14 (m, 3H, CH_3 acetyl), 2.08 (s, 3H, CH_3 acetyl), 2.05 (s, 3H, CH_3 acetyl), 0.92 (s, 3H, H-19), 0.88 (d, *J* = 6.3 Hz, 3H, H-21), 0.74 (s, 3H, H-18). **^{13}C NMR (100 MHz, $CDCl_3$)** δ(ppm) 34.6 C-1, 26.9 C-2, 74.1 C-3, 34.7 C-4, 41.0 C-5, 31.3 C-6, 70.7 C-7, 37.8 C-8, 28.9 C-9, 34.3 C-10, 25.6 C-11, 75.4 C-12, 45.1 C-13, 43.4 C-14, 22.9 C-15, 27.3 C-16, 47.7 C-17, 12.3 C-18, 22.6 C-19, 34.9 C-20, 17.9 C-21, 30.3 C-22, 35.6 C-23, 200.8 C-24, 21.4, 21.5, 21.6 CH_3 acetyl, 170–4, 170.5, 170.5 C═O acetyl, 137.0 ipso, 132.9 para, 128.6 meta, 128.0 ortho. MS (70 e$^-$V) 313 (16), 295 (16), 294 (12), 254 (19), 253 (91), 251 (15), 211 (12), 199 (12), 197 (11), 187 (12), 171 (13), 161 (15), 159 (18), 157 (15), 145 (18), 143 (17), 133 (11), 131 (11), 120 (19), 119 (11), 117 (12), 107 (15), 106 (10), 105 (100), 95 (11), 93 (15), 91 (19), 81 (14), 79 (15), 77 (30), 67 (11), 60 (11).

2.2. X-ray crystallography

Crystals of compounds **7a** and **8a** mounted on glass fiber were studied with an Oxford Diffraction Gemini "A" diffractometer with a CCD area detector ($\lambda_{MoK\alpha}$ = 0.71073 Å, monochromator: graphite) source equipped with a sealed tube X-ray source. Unit cell constants were determined with a set of 15/3 narrow frame/runs (1° in ω) scans. A data set consisted of 303 and 127 frames of

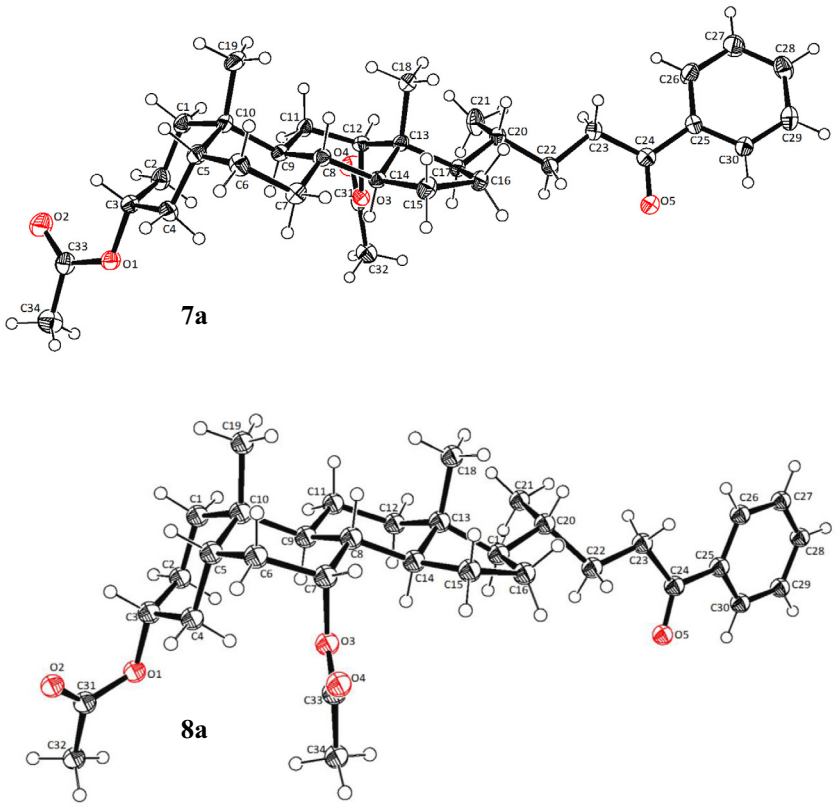


Fig. 2. Crystal structures of the 24-oxo-24-phenyl steroids **7a** and **8a** with the thermal ellipsoids drawn at 50% of probability.

intensity data collected for **7a** and **8a** respectively with a frame width of 1° in ω, a counting time of 5 s/frame, and a crystal-to-detector distance of 55.00 mm. The double pass method of scanning was used to exclude any noise. The collected frames were integrated by using an orientation matrix determined from the narrow frame scans.

CrysAlisPro and CrysAlis RED software packages [8] were used for data collection and data integration. Analysis of the integrated data did not reveal any decay. Final cell constants were determined by a global refinement of 3034 and 1886 reflections ($\theta < 26.7°$) for **7a** and **8a** respectively. Collected data were corrected for absorbance by using Analytical Numeric Absorption Correction [9] using a multifaceted crystal model based on expressions upon the Laue symmetry using equivalent reflections. Structure solution and refinement were carried out with the programs SHELXS97 and SHELXL97 [10]. Molecular graphics were generated with ORTEP-3 for Windows and the software used to prepare material for publication was WinGX [11].

Full-matrix least-squares refinement was carried out by minimizing $(Fo^2 - Fc^2)^2$. All non-hydrogen atoms were refined anisotropically. Hydrogen attached to carbon atoms were placed in geometrically idealized positions and refined as riding on their parent atoms, with C–H = 0.93–1.00 Å with U_{iso} (H) = 1.2U_{eq}(C) for aromatic, methylene and methyne groups, and U_{iso} (H) = 1.5 U_{eq}(C) for methyl group. Crystal data and experimental details of the structure determination are listed in Table 1 [12].

3. Results and discussion

Reaction of the acetylated bile acids with pivalic anhydride followed by palladium-catalyzed cross coupling with phenylboronic acid in THF, in the presence of tris-(4-methoxyphenyl)-phospine and water, afforded the corresponding 24-oxo-24-phenyl steroids in moderate to good yields (Scheme 2). All attempts at producing the cross coupling employing non acetylated bile acids were unsuccessful, presumably by consumption of the pivalic anhydride by reaction with the hydroxyl groups. The adequate conditions acid for the cross coupling were found to be [$Pd(CH_3COO)_2$ 0.045 mmol; pivalic anhydride 2.25 mmol; H_2O 3.75 mmol; phenylboronic acid 1.8 mmol, tris(p-metoxyphenyl)phosphine 0.105 mmol] × mmol after a series of iterative experiments in which the relation of substrate and each reagent were changed.

The introduction of the 24-phenyl-24-oxo moiety can be easily verified by the presence of the ^{1}H NMR signals associated to the phenyl group. In addition the signals of the diasterotopic pair of protons attached to C-23 characterize the NMR spectra of the obtained compounds (see Fig. 1 and Supplementary information file). The introduction of the 24-phenyl-24-oxo moiety only produces significant downfield shifts of the signals associated to C-23 and C-24 compared to those of the starting carboxylic acids (see Table 2 and Supplementary information file). In addition the presence of the ^{13}C signals associated to the aromatic ring characterizes the ^{13}C NMR spectra of the obtained ketones. The ^{1}H and ^{13}C resonance signals associated to the functionality present in the steroid framework confirm its integrity.

Finally X-ray studies conducted in monocrystals of compounds **7a** and **8a** confirmed the obtained structures (see Fig. 2).

4. Conclusion

In situ generation of mixed anhydrides derived from different acetylated bile acids and pivalic anhydride, followed by treatment with phenylboronic acid in the presence water, tris(p-metoxyphenyl)-phosphine and $Pd(CH_3COO)_2$ as catalyst, produced moderate to good yields of the corresponding 24-phenyl-24-oxo steroids. Although the obtained yield are slightly lower than those reported

for the previously reported acyl chloride-diphenylcadmium methodology, this one-pot palladium catalyzed procedure provides an attractive alternative that circumvents the inconveniences associated to the preparation and manipulation of steroid acyl chlorides and diphenylcadmium implied in the preceding protocol described for the preparation of the title compounds.

Acknowledgements

The authors thank to *Dirección General de Asuntos del Personal Académico* (DGAPA-UNAM) for financial support via project IN221911-3. M.C.M-T. thanks the Faculty of Chemistry (UNAM) for the scholarship granted under *Subprograma 127 Formación Básica en Investigación.* Thanks are due to Rosa I. del Villar Morales, Georgina Duarte Lisci (USAI-UNAM) for recording NMR and MS spectra. We want to express our gratitude to Dr. Carlos Cobas from Mestrelab® for assistance with the MestreNova NMR processing program.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.steroids.2013.07.008.

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[12] Crystallographic data form compounds have been deposited with the Cambridge Crystallographic Data Center as supplementary material numbers CCDC 938982 (7b) and 938963 (8b). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. E-mail:deposit@ccdc.cam.ac.uk.