Journal of the Mexican Chemical Society
ISSN: 1870-249X
editor.jmcs@gmail.com
Sociedad Química de México
México

Iglesias, Martín A.; Símuta Lopez, Eva M.; Xochihua Moreno, Sergio; Viñas Bravo, Omar; Montiel Smith, Sara; Meza Reyes, Socorro; Sandoval Ramirez, Jesús
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Journal of the Mexican Chemical Society, vol. 49, núm. 2, 2005, pp. 143-147
Sociedad Química de México
Distrito Federal, México

J. Mex. Chem. Soc. **2005,** *49(2),* 143-147.

J. Braz. Chem. Soc., Vol. 16, No. 3A, 381-385, 2
0103 - 5

A Convenient Procedure for the Synthesis of 3β-Hydroxy-6-oxo-5α-steroids. Application to t Synthesis of Laxogenin

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Uma rota conveniente para a síntese de 3β-hidroxi-6-oxo-5α-esteroides a partir de Δ^5-esteroides é descrita tendo sido aplicada para a síntese da laxogenina, substância que apresenta atividade como hormônio de crescimento vegetal. O método é uma alternativa para instalar este grupo funcional importante encontrado em esteróides naturais. O processo descrito utiliza reagentes baratos e pode ser executado em quatro etapas. As etapas de oxidação e de tratamento ácido não afetam a cadeia lateral espirocetálica presente na diosgenina (**16**).

A convenient pathway to obtain 3β-hydroxy-6-oxo-5α-steroids from 3β-acetoxy Δ^5-steroids is reported; the methodology was applied to the synthesis of laxogenin (**7**), substance that behaves as a plant growth hormone. This is an alternative way to produce an important functionality found in many examples of naturally occurring steroids. The developed procedure uses inexpensive reagents and can be carried out in four steps. The oxidizing and acidic steps used in this methodology did not affect the labile spiroketal side chain present in diosgenin (**16**).

Keywords: laxogenin, diastereoselective epoxidation, 3β-hydroxy-6-oxo-5α-steroids

Introduction

The 3β-hydroxy-6-oxo moiety is present in different naturally occurring steroids.[1] The brassinosteroid teasterone **(1),**[2] the steroid glycoside osladin **(2)**,[3] lactones as chiogralactone **(3)**[4] and dendrosterone **(4),**[5] and steroidal alkaloids like petisidine **(5)**[6] and petisine **(6)**[7] are some examples of naturally occurring steroids bearing such functionality (Figure 1).

Recently, we have synthesized laxogenin (**7**), a steroidal sapogenin isolated from *Smilax sieboldi*[8] and its C-23 substituted derivatives **8** and **9** and reported that they have shown plant growth promoting activity similar of that of brassinosteroids (Figure 2).[8] In that report, a protocol based on Brown´s hydroboration for the introduction of the 3β-hydroxy-6-oxo moiety was developed.

The 5β,6β-epoxy moiety has been previously used for the preparation of 6-oxosteroids. In particular, Henbest and Wrigley reported[9] that treatment of 5,6β-epoxy-5β-cholestan-3β-ol acetate with $BF_3 \cdot Et_2O$ led to corresponding 3β-acetoxy-5-fluoro-6β-hydroxy- steroid which was oxidized to 3β-acetoxy-5-fluoro cholestan-6-one using Jones reagent. More recently extension of this procedure to stigmasterol has been to obtain brassinosteroid analogues bearing the 5α-flu 6-oxo moiety.[9]

Owing our interest on steroids bearing s functionality, and after some reports on the hig stereoselective β-epoxidation of Δ^5-steroids using biph systems involving potassium permanganate and m salts,[10] we envisaged the β-epoxidation of the C5 double bond followed by the regioselective oxirane opening as the key steps for the introduction of an oxy atom at position C-6. This led us to an alternative prot for the synthesis of 3β-hydroxy-6-oxo steroids.

Results and Discussion

Treatment of cholesteryl acetate, in a mixtur

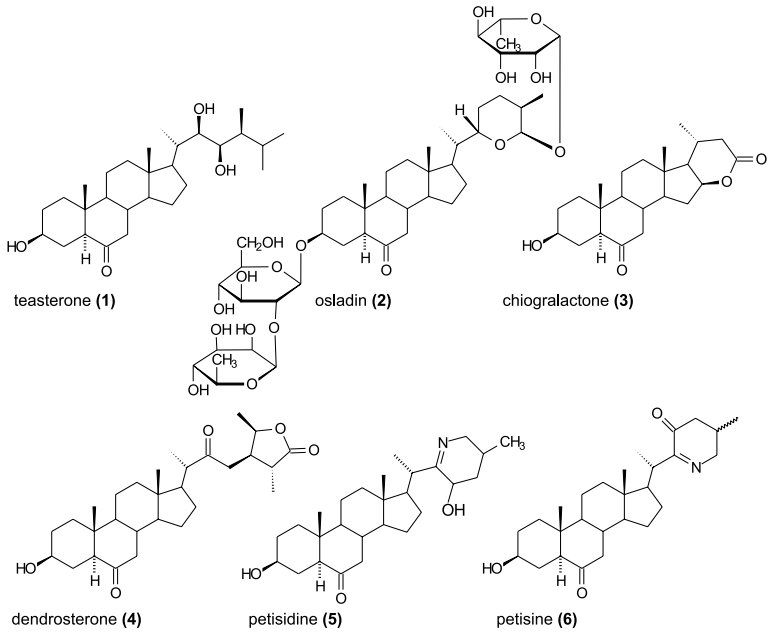


Figure 1. Some naturally occurring 3β-hydroxy-6-oxo-5α-steroids.

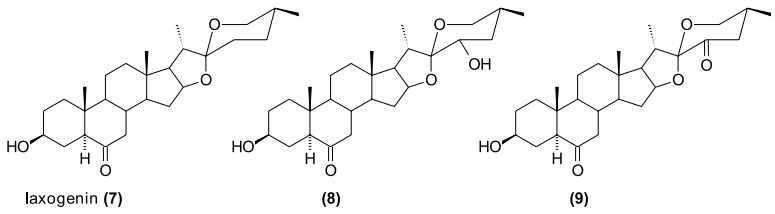
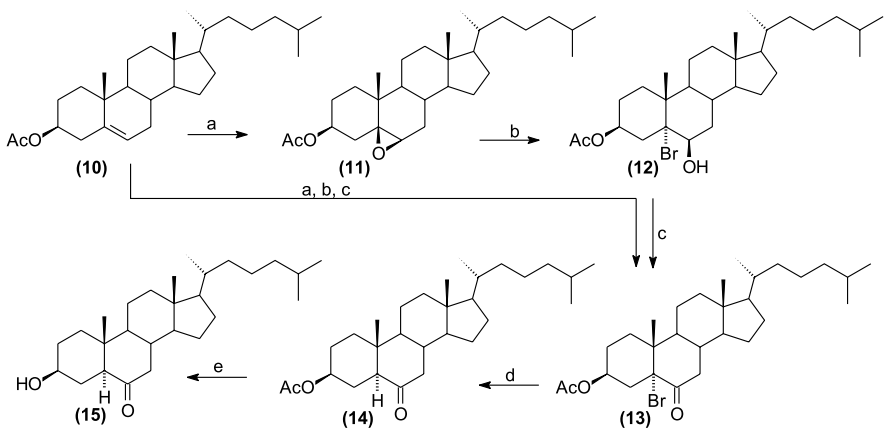


Figure 2. Laxogenin and 23-oxygenated derivatives with plant growth-promoting activity.

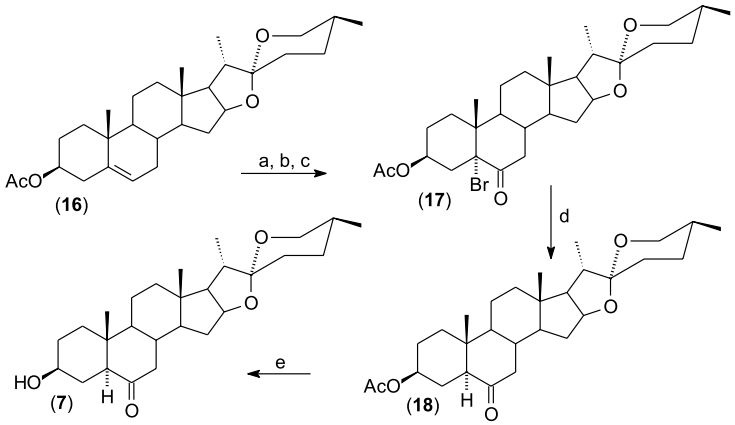
$Fe_2(SO_4)_3$ resulted in the highly diasteroselective β-epoxidation of the C5-C6 double bond; only traces of the α-epoxide could be detected in the ^{1}H NMR spectra. Regioselective opening of the β-oxirane ring with aq. HBr led to the bromohydrin **11** as sole product.

Treatment of the bromohydrin **12** with Jones reagent, supported on silica gel, led the bromoketone **13** (Scheme 1). In this way, manipulation of the reaction was rapidly effectuated and permitted a better treatment for wastes.

We also studied this three-reaction sequence without



a) $KMnO_4$, $Fe_2(SO_4)_3$, *tert*-BuOH, CH_2Cl_2, H_2O; b) HBr (aq), CH_2Cl_2;
c) CrO_3-silica gel, CH_2Cl_2; d) Zn, AcOH, reflux, e) KOH, MeOH



Scheme 2.

isolation of the intermediate epoxide **11** and bromohydrin **12**; this resulted in a very fast and convenient protocol for the conversion of cholesteryl acetate into the bromoketone **13** (75% overall yield for the consecutive three steps). Treatment of **13** with zinc in refluxing acetic acid yielded the acetylated ketone **14**, which on saponification afforded the desired 3β-hydroxy-5α-cholestan-6-one **(15)**.

The same one-pot synthetic sequence was applied to diosgenin acetate **(16)** to produce laxogenin **(7)**. Under these strong oxidizing and acidic media, the labile spiroketal side chain of diosgenin resulted unchanged (Scheme 2).

Experimental

NMR spectra were registered in $CDCl_3$ on a Varian Mercury spectrometer at 400 MHz for ^1H or 100 MHz for ^{13}C. Chemical shifts (δ) are expressed on ppm downfield from TMS. Melting points were obtained on a Gallenkamp MFB 595 apparatus and were not corrected.

*5,6β-Epoxy-5β-cholestan-3β-ol acetate (**11**)*

$KMnO_4$ (2 g) and $Fe_2(SO_4)_3.nH_2O$ (1 g) were finely grounded in a mortar, H_2O (0.2 mL) was added and the mixture was placed in a round bottom flask containing CH_2Cl_2 (5 mL). A solution of cholesteryl acetate **(10)** (428 mg, 1 mmol) in CH_2Cl_2 (5 mL) was added followed by addition of *tert*-butyl alcohol (0.5 mL). After 20 min of stirring at room temperature, the mixture was filtered through a pad of celite, and eluted with 30 mL of CH_2Cl_2. The crude filtrate was washed with H_2O (5x15) mL, dried (anhydrous Na_2SO_4) and evaporated to afford 427 mg (96%) of the desired epoxide **11**; mp 110-111 ºC, lit.[11] 112 ºC; ^1H NMR δ 4.76 (m, H-3), 3.07 (d. *J* 2.4 Hz, H 2.03 (s, C$\underline{H}_3$COO-3), 1.0 (s, CH_3-19), 0.89 (d, $J_{21\text{-}20}$ 6.8 CH_3-21), 0.86 (d, *J* 6.4 Hz, CH_3-26 and CH_3-27), 0.6 CH_3-18); ^{13}C NMR δ 29.76 C-1, 27.25 C-2, 71.28 38.02 C-4, 62.47 C-5, 63.55 C-6, 36.71 C-7, 32.49 56.13 C-9, 35.03 C-10, 21.99 C-11, 39.78 C-12, 42.2 13, 50.97 C-14, 24.23 C-15, 28.21 C-16, 56.13 C-17, 1 C-18, 17.11 C-19, 35.76 C-20, 18.7 C-21, 36.15 C 23.85 C-23, 39.51 C-24, 28.06 C-25, 22.64 C-26, 22.9 27, 21.41 $\underline{C}H_3$COO-3, 170.24 $CH_3\underline{C}$OO-3.

*5-Bromo-5α-cholestan-3β,6β-diol 3-acetate (**12**)*

A solution of the epoxide **11** (445 mg, 1 mmo CH_2Cl_2 (15 mL) was vigorously shaken for 5 min separatory funnel with 5 mL of 48% HBr. The org layer was washed with H_2O (5x 15 mL), dried (anh. Na_2 and evaporated to afford 510 mg (97%) of the bromohy **12**; mp 174-175 ºC, lit.[12] 177-179 ºC; ^1H NMR δ 5.47 H-3), 4.18 (s, H-6), 2.03 (s, C$\underline{H}_3$COO-3), 1.31 (s, CH_3- 0.90 (d, $J_{21\text{-}20}$ 6.6 Hz, CH_3-21), 0.86 (d, *J* 6.4 Hz, CH and CH_3-27), 0.67 (s, CH_3-18); ^{13}C NMR δ 35.16 C-1, 2 C-2, 72.17 C-3, 38.42 C-4, 86.73 C-5, 75.68 C-6, 34.6 7, 30.64 C-8, 47.44 C-9, 41.30 C-10, 21.39 C-11, 39.7 12, 42.72 C-13, 55.73 C-14, 24.16 C-15, 28.29 C-16, 5 C-17, 12.32 C-18, 18.15 C-19, 35.83 C-20, 18.78 C 36.18 C-22, 23.90 C-23, 39.51 C-24, 28.10 C-25, 22.6 26, 22.93 C-27, 21.50 $\underline{C}H_3$COO-3, 170.30 $CH_3\underline{C}$OO-

*3β-Acetoxy-5-bromo-5α-cholestan-6-one (**13**)*

A mixture of Jones reagent (2.5 mL) and silica gel (

was stirred until an homogeneous orange powder was formed. CH_2Cl_2 (15 mL) was added followed by the addition of a solution of the bromohydrin **12** (526 mg, 1 mmol) in CH_2Cl_2 (10 mL); the mixture was stirred for 20 min, filtered through an small pad of silica gel and the eluent was evaporated to afford 414 mg (79%) of the bromoketone **13**; mp 157-158 ºC (decomp.), lit.[13] 162 ºC (decomposition); ^{1}H NMR δ 5.32 (m, H-3), 3.15 (dd, $J_{7ax\text{-}7eq,\ 7ax\text{-}8ax}$ 14.85, 12.1 Hz, H-7a), 2.38 (ddd, $J_{4eq\text{-}4ax}$ 14.3, $J_{4eq\text{-}3ax}$ 4.2, $J_{4eq\text{-}2eq}$ 1.5 Hz, H-4eq), 2.28 (dd, $J_{7ax\text{-}7eq}$ 15, $J_{7eq\text{-}8ax}$ 5.5 Hz, H-7e), 2.03 (s, C<u>H</u>$_3$COO-3), 0.99 (s, CH_3-19), 0.90 (d, $J_{21\text{-}20}$ 6.2 Hz, CH_3-21), 0.86 and 0.85 (d, J 6.6 Hz, CH_3- 26 and 27), 0.65 (s, CH_3-18); ^{13}C NMR δ 30.43 C-1, 26.09 C-2, 70.92 C-3, 34.84 C-4, 79.61 C-5, 203.67 C-6, 40.45 C-7, 36.24 C-8, 47.26 C-9, 42.69 C-10, 21.79 C-11, 39.51 C-12, 43.03 C-13, 55.93 C-14, 23.84 C-15, 28.10 C-16, 56.16 C-17, 12.18 C-18, 14.59 C-19, 35.71 C-20, 18.72 C-21, 36.10 C-22, 23.84 C-23, 39.28 C-24, 28.07 C-25, 22.65 C-26, 22.90 C-27, 21.36 <u>C</u>H$_3$COO-3, 170.04 CH$_3$<u>C</u>OO-3.

*3β-Acetoxy-5-bromo-5α-cholestan-6-one (**13**) via a three steps procedure: β-epoxidation, oxirane-opening, alcohol-oxidation*

$KMnO_4$ (6 g) and $Fe_2(SO_4)_3.nH_2O$ (3 g) were finely grounded in a mortar, H_2O (0.6 mL) was added and the mixture was placed in a round bottom flask containing CH_2Cl_2 (45 mL). A solution of cholesteryl acetate **(10)** (1.284 g, 3 mmol) in CH_2Cl_2 (45 mL) was added followed by addition of *tert*-butyl alcohol (1.5 mL). After 20 min of stirring at room temperature, the mixture was filtered through a pad of celite and eluted with 30 mL of CH_2Cl_2. The crude filtrate was washed with H_2O (5x25 mL) and vigorously shaken for 5 min in a separatory funnel with 15 mL of 48% HBr, washed with H_2O (5x 30 mL) and added to a stirred mixture of silica gel-supported Jones Reagent (prepared from 2.5 mL of Jones reagent and 5 g silica gel as described for the oxidation of **12**) and CH_2Cl_2 (30 mL). The mixture was stirred for 20 min, filtered through a small pad of silica gel and the eluent was evaporated to afford 1.178 mg (75%) of the bromoketone **13**, identical as described above.

*3β-Acetoxy-5α-cholestan-6-one (**14**)*

A mixture of the bromoketone (524, 1 mmol), zinc powder (262 mg, 4 mmol) and acetic acid (10 mL) was stirred under reflux for 2 h. AcOEt (50 mL) was added and the mixture was washed with saturated NaCl solution (5x15 mL), 10% $NaHCO_3$ solution (3x20 mL) and H_2O (5x15 mL). The organic layer was dried with Na_2SO_4 and evaporated to afford 436 mg (98%) of the acetylated ketone **14**; mp 126-127 ºC, lit.[14] 128-129 ºC; ^{1}H NMR δ 4.67 (m, H-3), 2.03 (s, C<u>H</u>$_3$COO-3), 0.91 (d, $J_{21\text{-}20}$ 6.6 Hz, CH_3-21), 0.87 and 0.86 (d, J 6.6 Hz, CH_3-26 and CH_3-27), 0.77 (s, CH_3-19), 0.66 (s, CH_3-18); ^{13}C NMR δ 36.32 C-1, 26.75 C-2, 72.78 C-3, 26.04 C-4, 56.01 C-5, 210.40 C-6, 46.58 C-7, 37.85 C-8, 53.73 C-9, 40.87 C-10, 21.28 C-11, 39.38 C-12, 42.89 C-13, 56.59 C-14, 23.89 C-15, 27.97 C-16, 56.38 C-17, 11.94 C-18, 12.96 C-19, 35.62 C-20, 18.56 C-21, 36.00 C-22, 23.73 C-23, 39.38 C-24, 27.93 C-25, 22.48 C-26, 22.74 C-27, 21.39 <u>C</u>H$_3$COO-3, 170.56 CH$_3$<u>C</u>OO-3.

*3β-Hydroxy-5α-cholestan-6-one (**15**)*

A mixture of the acetylated ketone **14** (445 mg, 1 mmol), KOH (0.5 g) and MeOH (50 mL) was gently warmed for 15 min, H_2O (15 mL) was added, most of the MeOH was evaporated and the mixture was extracted with AcOEt (2x20 mL). The organic layer was washed with brine (3x15 mL) and H_2O, dried with $MgSO_4$ and evaporated to afford 412 mg (98%) of the hydroxylated ketone **15**; mp 141-142 ºC, lit.[15] 142-143 ºC; ^{1}H NMR δ 3.57 (m, H-3), 0.91 (d, $J_{21\text{-}20}$ 6.6 Hz, CH_3-21), 0.87 and 0.86 (d, J 6.6 Hz, CH_3-26 and CH_3-27), 0.75 (s, CH_3-19), 0.66 (s, CH_3-18); ^{13}C NMR δ 36.65 C-1, 30.61 C-2, 70.44 C-3, 29.97 C-4, 56.72 C-5, 210.87 C-6, 46.70 C-7, 37.92 C-8, 53.83 C-9, 40.96 C-10, 21.53 C-11, 39.44 C-12, 42.93 C-13, 56.66 C-14, 23.99 C-15, 28.03 C-16, 56.02 C-17, 12.06 C-18, 13.21 C-19, 35.68 C-20, 18.67 C-21, 36.07 C-22, 23.84 C-23, 39.44 C-24, 28.02 C-25, 22.60 C-26, 22.86 C-27.

*(25R)-3β-Acetoxy-5-bromo-5α-spirostan-6-one (**17**)*

Application of the described *one-pot β-epoxidation, oxirane-opening, alcohol-oxidation* procedure to diosgenin acetate **(16)** (1.370 g, 3 mmol) afforded 1.208 mg (73%) of the bromoketone **17**; mp 229-230 °C (petroleum ether/AcOEt), lit.[16] 230-233 °C; ^{1}H NMR δ 5.31 (m, H-3), 4.42 (ddd, $J_{16\text{-}17}$ $J_{16\text{-}15}$ 7.3 Hz, H-16), 3.48 (ddd, $J_{26ax\text{-}26eq}$ 11, $J_{26eq\text{-}25ax}$ 4.8, $J_{26eq\text{-}24eq}$ 1.8 Hz, H-26eq), 3.59 (dd, $J_{26ax\text{-}26eq}$ $J_{26ax\text{-}25ax}$ 11 Hz, H-26ax), 3.18 (dd, $J_{7ax\text{-}7eq}$ 11.7, $J_{7ax\text{-}8ax}$ 15 Hz, H-7α), 2.40 (ddd, $J_{4ax\text{-}4eq}$ 14.7, $J_{4eq\text{-}3ax}$ 5.3, $J_{4eq\text{-}2eq}$ 1.8 Hz, H-4α), 2.31 (dd, $J_{7ax\text{-}7eq}$ 15, $J_{7eq\text{-}8ax}$ 5.1 Hz, H-7β), 2.03 (s, C<u>H</u>$_3$COO-3), 1.01 (s, CH_3-19), 0.97 (d, $J_{20\text{-}21}$ 7 Hz, CH_3-21), 0.79 (d, $J_{25\text{-}27}$ 7 Hz, CH_3-27), 0.76 (s, CH_3-18); ^{13}C NMR δ 30.40 C-1, 36.05 C-2, 70.82 C-3, 34.80 C-4, 79.37 C-5, 203.21 C-6, 40.50 C-7, 35.74 C-8, 47.29 C-9, 42.68 C-10, 21.62 C-11, 39.25 C-12, 40.99 C-13, 55.88 C-14, 31.38 C-15, 80.34 C-16, 61.90 C-17, 16.55 C-18, 14.68 C-19, 41.60 C-20, 14.58 C.21, 109.14 C-22, 31.44 C-23, 28.80 C-24, 30.29 C-25, 66.83 C-26, 17.22 C-27, 170.02 CH$_3$COO-3, 21.35 CH$_3$COO-3.

*(25R)-3β-Acetoxy-5α-spirostan-6-one (**18**)*

1.103 g (2 mmol) of the bromoketone **17** were reduced as described for **13** to afford 756 mg (80%) of the ketone **20**; mp 223-224° (petroleum ether/AcOEt), lit.[16] 222-224 °C; ^{1}H NMR δ 4.66 (m, H-3), 4.41 (m, H-16), 3.47 (ddd, $J_{26ax\text{-}26eq}$ 11, $J_{26eq\text{-}25ax}$ 4.2, $J_{26eq\text{-}24eq}$ 1.8 Hz, H-26eq), 3.36 (dd, $J_{26ax\text{-}26e}$ $J_{26ax\text{-}25ax}$ 11 Hz, H-26ax.), 2.03 (s, C$\underline{H}_3$COO-3), 0.97 (d, $J_{21\text{-}20}$ 6.97 Hz, CH_3-21), 0.79 (d, $J_{27\text{-}25}$ 6.97 Hz, CH_3-27), 0.78 (s, CH_3-19), 0.78 (s, CH_3-18). ^{13}C NMR δ 36.35 C-1, 26.84 C-2, 72.66 C-3, 26.16 C-4, 56.35 C-5, 209.63 C-6, 46.68 C-7, 37.38 C-8, 53.71 C-9, 40.95 C-10, 21.36 C-11, 39.44 C-12, 40.92 C-13, 56.42 C-14, 31.58 C-15, 80.32 C-16, 61.96 C-17, 16.49 C-18, 13.18 C-19, 41.60 C-20, 14.56 C-21, 109.14 C-22, 31.34 C-23, 28.77 C-24, 30.29 C-25, 66.81 C-26, 17.21 C-27, 170.31 $CH_3\underline{C}OO$-3, 21.41 $\underline{C}H_3COO$-3.

*(25R)-3β-Hydroxy-5α-spirostan-6-one, laxogenin (**7**)*

473 mg (1 mmol) of the ketone **18** were hydrolyzed as described for **14** to afford 422 mg (98%) of laxogenin **(7)**; mp 210-211 °C (petroleum ether/AcOEt), $[\alpha]_D^{25}$ - 83 (*c* 1.1, $CHCl_3$); lit.[17] 210-212 °C; $[\alpha]_D^{25}$- 86 (c = 1.0, $CHCl_3$); ^{1}H NMR δ 4.41 (m, H-16), 3.57 (m, H-3), 3.47 (ddd, $J_{26ax\text{-}26eq}$ 11, $J_{26e\text{-}25ax}$ 4.2 and $J_{26eq\text{-}24eq}$ 1.8 Hz, H-26e), 3.36 (dd, $J_{26ax\text{-}26eq}$ and $J_{26ax\text{-}25ax}$ 11 Hz, H-26ax.), 0.97 (d, $J_{21\text{-}20}$ 6.97 Hz, CH_3-21), 0.79 (d, $J_{27\text{-}25}$ 6.97 Hz, CH_3-27), 0.78 (s, CH_3-19), 0.78 (s, CH_3-18); ^{13}C NMR δ 36.59 C-1, 30.56 C-2, 70.27 C-3, 29.91 C-4, 56.70 C-5, 210.39 C-6, 46.68 C-7, 37.33 C-8, 53.79 C-9, 40.90 C-10, 21.36 C-11, 39.46 C-12, 40.90 C-13, 56.39 C-14, 31.53 C-15, 80.31 C-16, 61.91 C-17, 16.43 C-18, 13.26 C-19, 41.55 C-20, 14.50 C-21, 109.11 C-22, 31.29 C-23, 28.71 C-24, 30.21 C-25, 66.75 C-26, 17.14 C-27.

Conclusions

A convenient procedure to generate 3β-hydroxy-6-oxo-5α-steroids from Δ^5-unsaturated steroids has been accomplished through a four steps process; the three first steps can be effectuated in a one-pot manner. Each step has been performed obtaining a good overall yield.

Acknowledgments

We are indebted to CONACyT, Mexico, for financial support via grant 35235-E and the scholarships granted to S.X.M and O.V.B. We also want to acknowledge Professor Benjamín Ruiz for laboratory facilities at the Facultad de Química of UNAM.

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Received: June 24,
Published on the web: March 30,