Optimal TBHP Allylic Oxidation of Δ^5-Steroids Catalyzed by Dirhodium Caprolactamate

Hojae Choi and Michael P. Doyle*

Department of Chemistry and Biochemistry, University of Maryland, College Park, Maryland 20742

mdoyle@umd.edu

Received Date (will be automatically inserted after manuscript is accepted)

Supporting Information

General. All reagents were obtained commercially, unless otherwise noted, and were purified according to the guidelines of Armarego and Chai.[1] Yields reported are for isolated mass yields after chromatography. 70 % *tert*-Butyl hydrogen peroxide in water (T-HYDRO®) was purchased from Aldrich. The preparation of dirhodium(II) caprolactamate [$Rh_2(cap)_4$•$2CH_3CN$] from rhodium acetate has been previously described.[2] ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were obtained on a Bruker DRX-400 NMR spectrometer as solutions in $CDCl_3$. Chemical shifts are reported in parts per million (ppm, δ) downfield from Me_4Si (TMS); coupling constants are reported in Hertz (Hz). Thin layer chromatography (TLC) was performed on Merck 0.25 mm silica gel 60 F_{254} plates with visualization by fluorescence quenching or vanillin stain. Chromatographic purification and filtration were performed using SiliCycle (60Å, 40-63 mesh) silica gel.

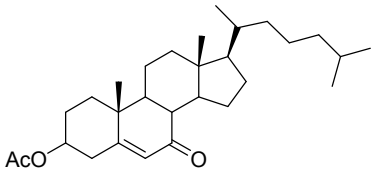
---

[1] Armarego, W. L. F.; Chai, C. L. L. *Purification of Laboratory Chemicals*; 5th ed., Elsevier Science: New York, 2003.

[2] Doyle, M. P.; Westrum, L. J.; Wolthuis, W. N. E.; See, M. M.; Boone, W. P.; Bagheri, V.; Pearson, M. M. *J. Am. Chem. Soc.* **1993**, *115*, 958.

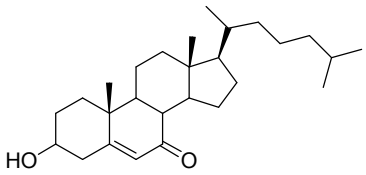
Representative Procedure [1.0 mol% $Rh_2(cap)_4$]. Substrate (0.81 mmol, 1.0 equiv) and $Rh_2(cap)_4$ (6 mg, 0.0081 mmols, 0.01 equiv) were added to a 10-mL vial equipped with a magnetic stir bar. Solvent (3 mL, 0.27 M) was added followed by T-HYDRO® (70 % solution in water, 4.07 mmol, 5.0 equiv) via syringe all at once. The vial was loosely capped to limit solvent evaporation and stirred for 20 hrs at 40 °C. The mixture was concentrated under reduced pressure and then purified by column chromatography (1 cm diameter, 15 cm long glass column, hexane/ethyl acetate).

Representative Procedure [0.1 mol% $Rh_2(cap)_4$]. Substrate (2.72 mmols, 1.0 equiv) and $Rh_2(cap)_4$ (2 mg, 0.0027 mmols, 0.001 equiv) were added to a 10-mL vial equipped with a magnetic stir bar. Solvent (2 mL, 1.36 M) was added followed by the addition of T-Hydro® (70 % solution in water, 21.7 mmols, 8.0 equiv) via syringe all at once. As in the previous procedure, the vial was loosely capped to limit solvent evaporation and stirred for 20 hrs at 40 °C. The mixture was concentrated under reduced pressure and then purified by column chromatography (3 cm diameter, 15 cm long glass column, hexane/ethyl acetate).

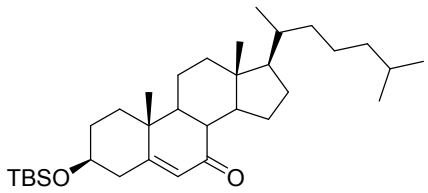


3β-Acetoxycholest-5-ene-7-one (8, Z = OAc). R_f = 0.50 (Hexane : EtOAc = 3:1). mp 158-160 °C (lit. mp 155-157 °C).[6] IR (solid) 1728, 1671 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.70 (d, *J* = 1.6 Hz, 1H), 4.76-4.67 (m, 1H), 2.58-1.00 (comp, 26H), 2.05 (s, 3H), 1.21 (s, 3H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 3H), 0.86 (d, *J* = 6.6 Hz, 3H), 0.68 (s, 3H) . ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.8, 170.1, 163.8, 126.6, 72.1, 54.7, 49.8, 49.7, 45.3, 43.0, 39.4, 38.6, 38.2, 37.6, 36.1, 35.9, 35.6, 28.4, 27.9, 27.2, 26.2, 23.7, 22.7, 22.5, 21.1, 21.1, 18.8, 17.1, 11.9. ^1H, ^{13}C NMR, and IR data were in accordance with literature values. [3]

[3] Shing, T. K. M.; Yeung, Y.; Su, P. L. *Org. Lett.* **2006**, *8*, 3149.

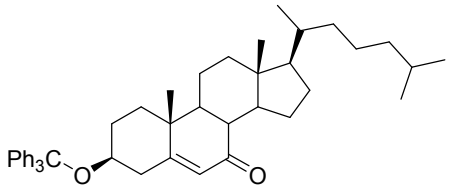


3β-Hydroxycholest-5-ene-7-one (8, Z = OH). R_f = 0.25 (Hexane : EtOAc = 2:1). mp 168-170 °C (lit. mp 169-171 °C).[4a] IR (solid) 1669 cm^{-1} , ^1H NMR (400 MHz, $CDCl_3$): δ 5.69 (d, *J* = 1.6 Hz, 1H), 3.70-3.64 (m, 1H), 2.54-0.99 (comp, 26H), 1.20 (s, 3H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 3H), 0.86 (d, *J* = 6.6 Hz, 3H), 0.68 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.5, 165.3, 129.0, 70.4, 54.8, 49.9, 49.8, 45.4, 43.1, 41.8, 39.4, 38.7, 38.3, 36.3, 36.1, 35.7, 31.1, 28.5, 28.0, 26.3, 23.8, 22.8, 22.5, 21.2, 18.8, 17.3, 12.0. ^1H, ^{13}C NMR, and IR data were in accordance with literature values.[4b]

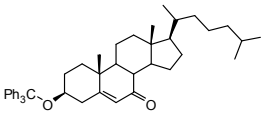


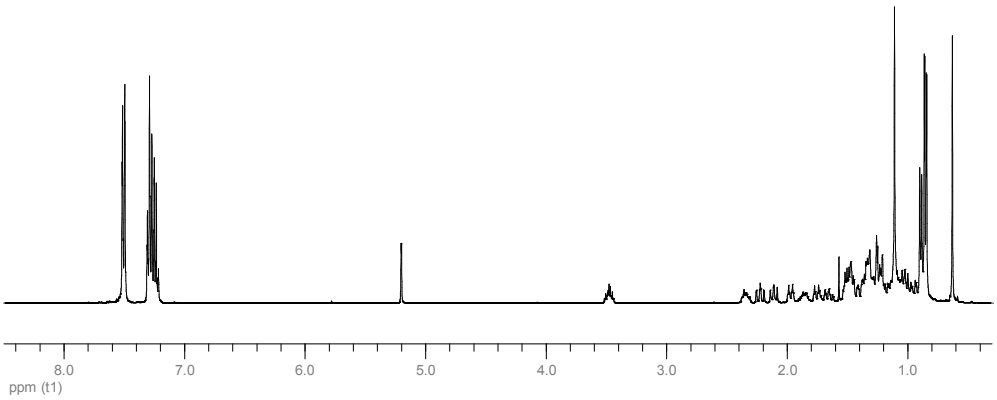
3β-[(1,1-dimethylethyl)dimethylsilyl]oxycholest-5-ene-7-one (8, Z = OTBS) . R_f = 0.80 (Hexane : EtOAc = 5:1). m.p. 213-215 °C (lit. mp 215-216 °C).[5] IR (solid) 1666 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.66 (d, *J* = 1.3 Hz, 1H), 3.567-3.59 (m, 1H), 2.48-1.07 (comp, 26H), 1.19 (s, 3H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.89 (s, 9H), 0.87 (d, *J* = 6.6 Hz, 3H), 0.86 (d, *J* = 6.6 Hz, 3H), 0.68 (s, 3H), 0.09 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.4, 165.8, 125.7, 71.3, 54.7, 49.9, 49.9, 45.3, 43.0, 42.5, 39.4, 38.7, 38.3, 36.4, 36.1, 35.6, 31.7, 28.5, 27.9, 26.3, 25.8, 23.8, 22.8, 22.5, 21.1, 18.8, 18.1, 17.2, 11.9, -4.6, -4.6. ^1H, ^{13}C NMR, and IR data were in accordance with literature values.[3]

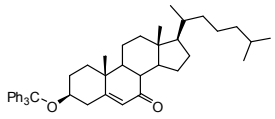
[4] (a) Marwah, P.; Marwah, A.; Lardy, H. A. *Green Chem.* **2004**, *6*, 570. (b) Brunel, J. M.; Loncle, C.; Vidal, N.; Dherbomez, M.; Letourneux, Y. *Steroids* **2005**, *70*, 907.
[5] Ciuffreda, P.; Casati, S.; Bollini, D.; Santaniello, E. *Steroids* **2003**, *68,* 193.

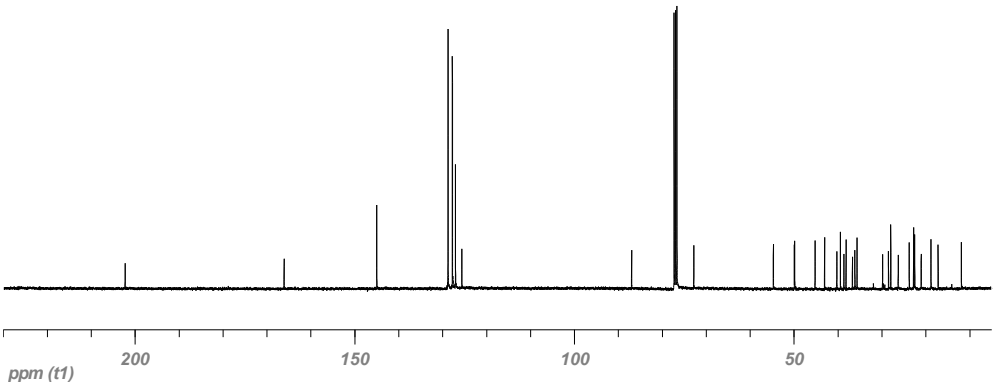


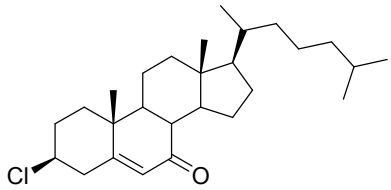
3β-triphenylmethyloxycholest-5-ene-7-one (8, Z = $OCPh_3$). R_f = 0.75 (Hexane : EtOAc = 5:1). m.p. 187-189 °C. IR (solid) 1672 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.52-7.49 (comp, 6H), 7.31-7.24 (comp, 9H), 5.66 (d, *J* = 1.3 Hz, 1H), 3.52-3.44 (m, 1H), 2.36-0.95 (comp, 26H), 1.11 (s, 3H), 0.89 (d, *J* = 6.5 Hz, 3H), 0.86 (d, *J* = 6.6 Hz, 3H), 0.85 (d, *J* = 6.6 Hz, 3H), 0.63 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.3, 166.1, 145.0, 128.7, 127.7, 127.0, 125.6, 86.9, 72.8, 54.7, 49.9, 49.8, 45.2, 43.0, 40.2, 39.4, 38.6, 38.1, 36.7, 36.1, 35.6, 29.8, 28.5, 27.9, 26.2, 23.7, 22.7, 22.5, 21.0, 18.8, 17.2, 11.9. HRMS (EI) calcd for $C_{46}H_{58}O_2$ 642.4437, found 643.4499 $(M+H)^+$.





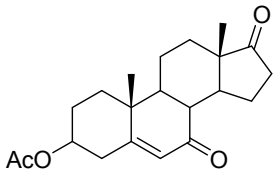




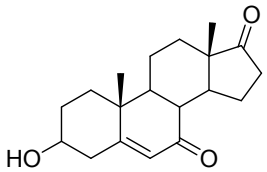


3β-Chlorocholest-5-ene-7-one (8, Z = Cl). R_f = 0.80 (Hexane : EtOAc = 5:1). mp 143-144 °C (lit. mp 145 °C).[6] IR (solid) 1666 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.68 (s, 1H), 3.86-3.82 (m, 1H), 2.70 (d, *J* = 8.3 Hz, 2H), 2.43-2.36 (m, 1H), 2.26-2.15 (comp, 2H), 2.05-1.88 (comp, 4H), 1.57-1.04 (comp, 20H), 1.22 (s, 3H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 3H), 0.86 (d, *J* = 6.6 Hz, 3H), 0.68 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.9, 163.8, 126.1, 57.7, 54.7, 49.8, 49.7, 45.4, 43.0, 42.6, 39.4, 38.6, 38.0, 36.1, 35.6, 32.7, 28.5, 27.9, 26.2, 23.8, 22.7, 22.5, 21.0, 18.8, 17.2, 11.9. ^1H, ^{13}C NMR, and IR data were in accordance with literature values.[6]

[6] Shafiullah, K.; Ejaz , A.; Ogura, H.; Takayanagi, H. *J. Chem. Soc., Perkin Trans. 1*, **1979**, 2727**.**

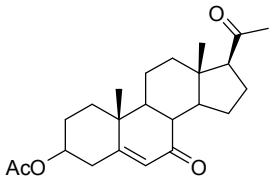


3β-Acetoxyandrost-5-ene-7.17-dione (9a). R_f = 0.45 (Hexane : EtOAc = 2:1). mp 187-189 °C (lit. mp 184-185 °C).[7] IR (solid) 1739, 1726, 1671 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.76 (d, *J* = 1.8 Hz, 1H), 4.69-4.77 (m, 1H), 2.79-2.85 (m, 1H), 2.63-2.38 (comp, 4H), 2.06 (s, 3H), 2.19-1.23 (comp, 12H), 1.24 (s, 3H), 0.90 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 220.1, 200.6, 170.1, 164.7, 126.4, 71.8, 49.9, 47.7, 45.6, 44.2, 38.3, 37.7, 35.9, 35.5, 30.6, 27.2, 24.1, 21.1, 20.4, 17.3, 13.6. ^1H, ^{13}C NMR, and IR data were in accordance with literature values.[3]

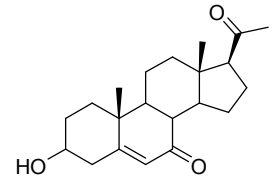


3β-Hydroxyandrost-5-ene-7.17-dione (9b). R_f = 0.20 (Hexane : EtOAc = 1:1). mp 236-238 °C (lit. mp 229-232 °C).[6] IR (solid) 1727, 1671 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.75 (d, *J* = 1.7 Hz, 1H), 3.66-3.74 (m, 1H), 2.78-2.85 (m, 1H), 2.33-2.62 (comp, 4H), 2.19-1.21 (comp, 13H), 1.23 (s, 3H), 0.90 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 220.4, 201.1, 166.2, 125.8, 70.2, 50.0, 47.8, 45.7, 44.3, 41.8, 38.3, 36.2, 35.6, 31.0, 30.6, 24.1, 20.5, 17.4, 13.7. ^1H, ^{13}C NMR, and IR data were in accordance with literature values.[8]

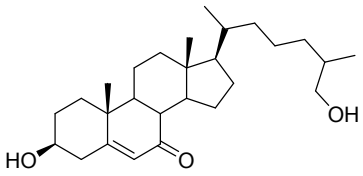
[7] Arsenou, E. S.; Koutsourea, A. I.; Fousteris, M. A.; Nikolaropoulos, S. S. *Steoroids* **2003**, *68*, 407.
[8] Silvestre, S. M.; Salvador, J. A. R. *Tetrahedron* **2007**, *63*, 2439.



3β-Acetoxypregn-5-ene-7,20-dione (10a). R_f = 0.40 (Hexane : EtOAc = 2:1). mp 140-141 °C (lit. mp 141-142 °C).[3] IR (solid) 1705, 1725, 1670 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.73 (d, *J* = 1.6 Hz, 1H), 4.75-4.69 (m, 1H), 2.60-1.26 (comp, 18H), 2.13 (s, 3H), 2.06 (s, 3H), 1.22 (s, 3H), 0.66 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 209.6, 201.1, 170.2, 164.1, 126.4, 72.0, 62.2, 49.9, 49.6, 45.2, 44.3, 38.3, 37.7, 37.6, 35.9, 31.6, 27.2, 26.4, 23.5, 21.2, 21.0, 17.2, 13.2. ^1H, ^{13}C NMR and IR data were in accordance with literature values.[3]



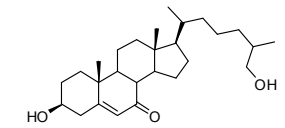
3β-Hydroxypregn-5-ene-7,20-dione (10b). R_f = 0.30 (Hexane : EtOAc = 1:1). mp 207-208 °C (lit. mp 209-210 °C).[9a] IR (solid) 1684, 1663 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.67 (d, *J* = 1.6 Hz, 1H), 3.67-3.62 (m, 1H), 2.51-1.17 (comp, 19H), 2.10 (s, 3H), 1.17 (s, 3H), 0.62 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 209.8, 201.5, 165.6, 125.7, 70.3, 62.2, 49.9, 49.7, 45.1, 44.3, 41.7, 38.3, 37.6, 36.3, 31.5, 31.0, 26.4, 23.5, 21.0, 17.2, 13.2. ^1H, ^{13}C NMR and IR data were in accordance with literature values.[9b]

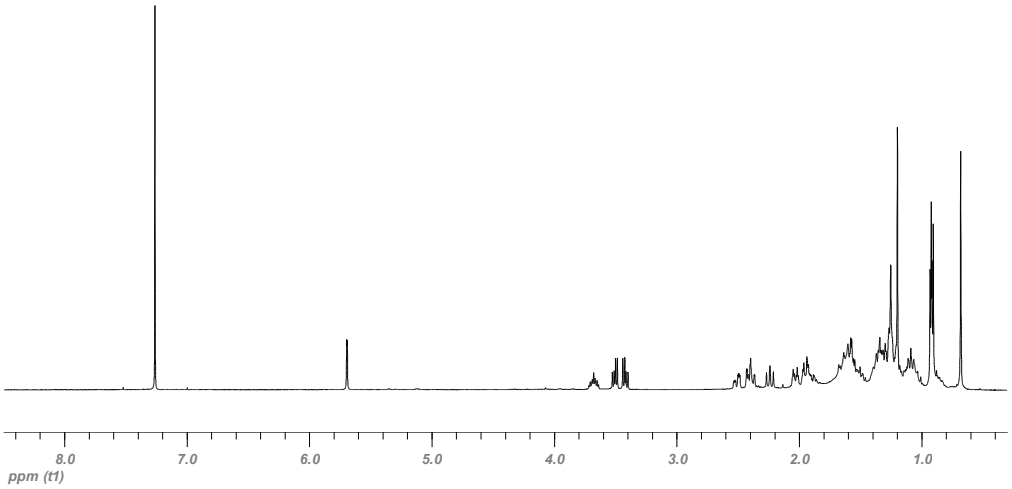


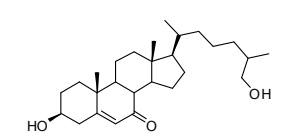
3β,27-Dihydroxycholest-5-ene-7-one (11). R_f = 0.35 (EtOAc). mp 144-145 °C . IR (solid) 1667 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.69 (d, *J* = 1.6 Hz, 1H), 3.68 (m, 1H), 3.51 (dd, *J* = 10.4, 5.9, 1H), 3.42 (dd, *J* = 10.4, 6.5, 1H), 2.54-1.03 (m, 25H), 1.20 (s, 3H), 0.93 (d, *J* = 6.5 Hz, 3H), 0.92 (d, *J* = 6.7 Hz, 3H), 0.68 (s, 3H). ^{13}C NMR (100

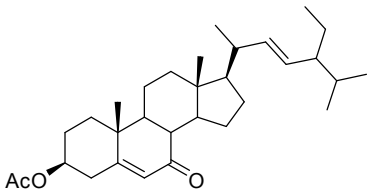
[9] (a) Marshall, C. W.; Ray, R. E.; Laos, I.; Riegel, B. *J. Am. Chem. Soc.* **1957**, *79*, 6303. (b) Jankowski, K.; Selye,H. *Steroids*, **1972**, *19*, 189.

MHz, $CDCl_3$): δ 202.2, 165.0, 126.1, 70.5, 68.5, 54.7, 49.9, 49.8, 45.3, 43.0, 41.7, 38.6, 38.2, 36.3, 36.1, 35.7, 35.6, 33.4, 31.1, 28.5, 26.3, 23.4, 21.2, 18.8, 17.3, 16.4, 11.9. HRMS (EI) calcd for $C_{46}H_{58}O_2$ 416.3290 ($M + H^+$), found 417.3377 $(M + H)^+$.

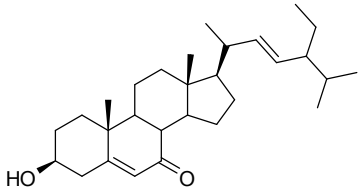








3β-Acetoxystigmasta-5,22-diene-7-one (12a). R_f = 0.60 (Hexane : EtOAc = 3:1). mp 182-183 °C (lit. mp 185 °C).[10] IR (solid) 1731, 1669 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.70 (d, *J* = 1.5 Hz, 1H),, 5.18 (dd, *J* = 15.2 Hz, *J* = 8.6 Hz), 5.02 (dd, *J* = 15.2 Hz, *J* = 8.7 Hz), 4.76-4.68 (m, 1H), 2.58-1.13 (comp, 23H), 2.05 (s, 3H), 1.21 (s, 3H), 1.03 (d, *J* = 6.6 Hz, 3H), 0.85 (d, *J* = 6.3 Hz, 3H), 0.82-0.79 (comp, 6H) 0.70 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.8, 170.2, 163.7, 138.0, 129.4, 126.6, 72.1, 54.6, 51.1, 49.9, 49.7, 45.3, 42.9, 40.2, 38.5, 38.3, 37.7, 35.9, 31.8, 29.0, 27.3, 26.3, 25.3, 21.4, 21.2, 21.1, 21.0, 18.9, 17.2, 12.2, 12.1. ^1H, ^{13}C NMR and IR data were in accordance with literature values.[10]



3β-Hydroxystigmasta-5,22-diene-7-one (12b). R_f = 0.40 (Hexane : EtOAc = 2:1). mp 142-144 °C (lit. mp 144 °C).[11] IR (solid) 1676 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.66 (d, *J* = 1.5 Hz, 1H),, 5.14 (dd, *J* = 15.2 Hz, *J* = 8.6 Hz), 5.00 (dd, *J* = 15.2 Hz, *J* = 8.7 Hz), 3.67-3.60 (m, 1H), 2.51-1.10 (m, 24H), 1.17 (s, 3H), 1.00 (d, *J* = 6.6 Hz, 3H), 0.82 (d, *J* = 6.4 Hz,3H), 0.76-0.79 (comp, 6H) 0.67 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.3, 165.2, 138.0, 129.4, 126.0, 70.4, 54.6, 51.1, 49.9, 49.8, 45.3, 42.9, 41.7, 40.2, 38.5, 38.2, 36.3, 31.8, 31.1, 29.0, 26.3, 25.3, 21.3, 21.1, 21.0, 18.9, 17.2, 12.2, 12.1. ^1H, ^{13}C NMR and IR data were in accordance with literature values.[11]

[10] Pearson, A. J.; Chen, Y.; Han, G. R.; Hsu, S.; Ray, T. *J. Chem. Soc. Perkin Trans. 1* **1985**, 267.
[11] Shu, Y.; Jones, S. R.; Kinney, W. A.; Selinsky, B. S. *Steroids* **2002**, *67*, 291.