Revised Structures for the Lactones Obtained by Reduction of the Adduct of Ergosterol Acetate with Maleic Anhydride

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Introduction

In the course of work aimed at the synthesis of various congeners of brassinolide,[1] a naturally occurring steroid lactone functioning as a plant hormone,[2a−c] we considered the possibility of adding a five-membered lactone to ring B of a steroid by metal hydride reduction of the cyclic anhydride **1a** (Inhoffen adduct) obtained by the Diels−Alder reaction of ergosteryl acetate with maleic anhydride.[3,4]

According to the literature,[5,6a] anhydride **1a** is selectively reduced by sodium borohydride to 3β-acetoxy lactone **2a** and by lithium aluminum hydride to the corresponding hydroxy lactone **2b**, none of the isomeric lactones **3a** or **3b** being obtained. This, together with the evidence that the methoxyanhydride **1c**, under similar conditions, afforded both methoxy lactones **2c** and **3c** in a 1:1 ratio,[6b] led to the suggestion that the reduction of the anhydride carbonyl more remote from C-3 is due to complexation of the less hindered carbonyl group with the reagent cation and the acetate carbonyl group at C-3 (Figure 1).[5,6a]

The work described in this note shows that the structures of lactones of type **2** and **3** should be reversed and the proposed mechanism reconsidered.

Results and Discussion

Reduction of the acetoxy anhydride **1a** or of the hydroxy anhydride **1b** with $LiAlH_4$ under the reported conditions[5] affords a lactone with the same properties as reported earlier (mp, rotation) but with structure **3b** rather than **2b**, on the basis of the ^{1}H-NMR (500 MHz) spectra of **3b**, the corresponding 2,2,2′,4,4-pentadeuterated[7] compound **3d** and the related 3-ketones **3e** and **3f** (Table 1). Assignments in the spectra of these compounds were made by standard 1D and 2D NMR techniques, such as NOE, HOHAHA,[8] COSY,[9] and NOESY[10]

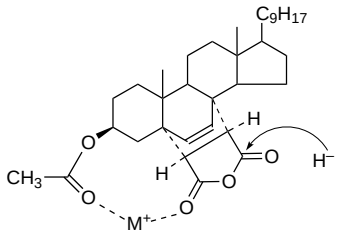
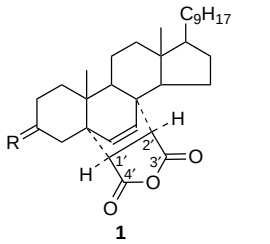


Figure 1.

experiments. The reason for the earlier incorrect structure attribution is an erroneous assignment of a (*dddd*) centered at δ 2.56 which is also present in the spectra of the other lactones of type **3** and which in a 100 MHz ^{1}H NMR spectrum[5,6] appears as a multiplet. In the earlier work[5] this signal was assigned to H-4α while we have found that it is due to H-15α which is deshielded by the C-3′ lactone carbonyl. The proton responsible for this signal is not coupled with the H-3α which resonates at δ 3.89. The assignment of the δ 2.56 signal to H-15α was substantiated in **3a** by a HOHAHA experiment which showed that it was correlated with the 21-methyl (δ 0.99, d, J = 7.0 Hz). The 3α proton, in turn, was coupled with the 4β and 4α protons at δ 1.90 and 1.86 in the spectrum of **3b** (in the spectrum of **3a** the 3α proton resonates at δ 4.93 and is coupled with the 4β and 4α protons resonating at δ 1.97 and 1.88, respectively). The latter are absent in the spectra of the 2,2,2′,4,4-pentadeuterated lactone **3d** and in that of the 2,2,2′,4,4-pentadeuterated ketone **3f** and appear at lower field (at δ 2.91 and 2.31) in the spectrum of the keto lactone **3e** where they flank the signal due to H-15α. Finally the signal of H-3α has a normal chemical shift at δ 3.88 in the spectrum of **3b** and **3d** and is not deshielded by a carbonyl group.



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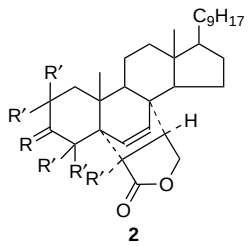

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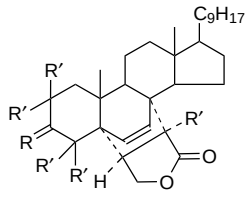

3

a, R = H, βOAc; R′ = H
b, R = H, βOH; R′ = H
c, R = H, βOMe; R′ = H
d, R = H, βOH; R′ = D
e, R = O; R′ = H
f, R = O; R′ = D

Support for our structure assignment was produced by synthesis of the true hydroxy lactone **2b** by oxidation

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(6) (a) Burke, D. E.; Le Quesne, P. W. *J. Org. Chem.* **1971**, *36*, 2397. (b) This ratio appears in the experimental of ref 6. In the discussion a 13:1 ratio was reported.
(7) The deuteration was performed as reported for other steroids. (Anastasia, M.; Allevi, P.; Fiecchi, A.; Galli, G.; Gariboldi, P.; Scala, A. *J. Org. Chem.* **1983**, *48*, 686).
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(9) Aue, W. P.; Bartholdi, E.; Ernst, R. R. *J. Chem. Phys.* **1976**, *64*, 2229.
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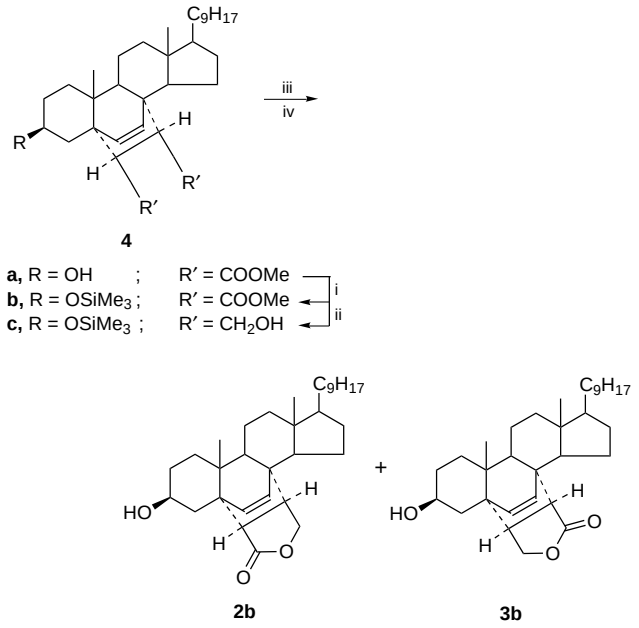
Table 1. ^{1}H Assignments of Lactones 3a−f

	^{1}H[a]				
proton(s)	lactone **3a** δ (ppm) mult, *J* (Hz)	lactone **3b** δ (ppm) mult, *J* (Hz)	lactone **3d** δ (ppm) mult, *J* (Hz)	lactone **3e** δ (ppm) mult, *J* (Hz)	lactone **3f** δ (ppm) mult, *J* (Hz)
3α-H	4.93 dddd, 5.6, 6.3, 11.2, 11.2	3.89 dddd, 5.6, 6.3, 11.2, 11.2	3.88 s		
4α-H	1.88[b] dd, 5.6, 13.3	1.86[b] ddd, 5.6, 13.3	absent	2.31[c] dd, 2.1, 15.4	absent
4β-H	1.97[b] dd, 11.2, 13.3	1.90[b] dd, 11.2, 13.3	absent	2.91[c] d, 15.4	absent
6-H	5.74 d, 9.1	5.77 d, 9,1	5.77 d, 9.1	5.83 d, 9.1	5.83 d, 9.1
7-H	6.23 d, 9.1	6.22 d, 9.1	6.22 d, 9.1	6.30 d, 9.1	6.30 d, 9.1
15α-H	2.56 dddd, 3.5, 7.0, 9.8, 12.6	2.56 dddd, 3.5, 7.0, 9.8, 12.6	2.56 dddd, 3.5, 7.0, 9.8, 12.6	2.55 overlapped	2.55 dddd, 3.5, 7.0, 9.8, 12.6
18-Me	0.70 s	0.71 s	0.71 s	0.75 s	0.75 s
19-Me	0.90 s	0.89 s	0.89 s	1.10 s	1.10 s
22-H and 23-H	5.14−5.22 m	5.14−5.22 m	5.14−5.22 m	5.14−5.22 m	5.14−5.22 m
1′-H	3.17 ddd, 5.6, 9.1, 10.5	3.10 ddd, 5.6, 9.1, 10.5	3.09 dd, 5.6, 9.1	2.84 ddd, 5.6, 9.1, 10.5	2.84 dd, 5.6, 9.1
2′-H	2.43 d, 10.5	2.41 d, 10.5	absent	2.41 d, 10.5	absent
4′α-H	3.81 dd, 5.6, 9.1	3.83 dd, 5.6, 9.1	3.82 dd, 5.6, 9.1	3.72 dd, 5.6, 9.1	3.72 dd, 5.6, 9.1
4′β-H	4.22 dd, 9.1, 9.1	4.16 dd, 9.1, 9.1	4.16 dd, 9.1, 9.1	4.14 dd, 9.1, 9.1	4.14 dd, 9.1, 9.1

[a] Chemical shifts taken from the 1D proton spectrum whenever possible: s, singlet; d, doublet; m, multiplet. [b] Taken from the HOHAHA spectrum. [c] α and β assignements derived from the relative NOE.

Scheme 1[a]



[a] (i) Me_3SiCl, Et_3N; (ii) $LiAlH_4$; (iii) Ag_2CO_3−Celite; (iv) HCOOH, MeOH.

with Ag_2CO_3[11] of 3β-(trimethylsilyl)oxy diol **4c**, prepared from the known[4] 3β-hydroxy-(1′β,2′β-dimethoxycarbonyl)-5α,8α-ethanoergosta-6,22-diene (**4a**) by the reactions shown in Scheme 1.

The ^{1}H-NMR spectrum of this lactone shows diagnostic signals (Table 2) at δ 2.62, for the 4α proton, deshielded by the lactonic carbonyl, and at δ 1.79 for the 4β proton. Both these protons are coupled with the 3α proton, which resonates at δ 4.17 since is deshielded by the lactonic carbonyl. They are shifted to lower field (δ 3.55 and 2.67) in the spectrum of the ketone **2e** and are absent in the spectrum of the 2,2,2′,4,4-pentadeuterated keto lactone **2f**. Since the 15α proton is not deshielded, its signal, in the ^{1}HNMR spectrum of **2b**, is within the envelope of the methylene signals at high fields. A signal is however present at δ 2.47 due to the 2′ proton. This signal is also present in the spectrum of lactone **2e** and **2f**, but its multiplicity is simplified in the spectrum of **2f** since a deuterium atom is present at C-1′ of this deuterated lactone.

As a consequence of the change in structure of the lactone obtained by reduction of the Inhoffen adduct of ergosterol with maleic anhydride, a different explanation for the selectivity should be found.

Experimental Section

The ^{1}H NMR spectra (500.13 MHz) were recorded in $CDCl_3$ at 303 K and were referenced to $CHCl_3$ at 7.24 ppm. TLC was carried out on silica gel 60 F_{254} microplates. All known compounds (**1a**, **1b**, **3a**, **3b**, **3e**, and **4a**) were prepared according to previous reports.[4−6] Usual workup refers to dilution with water, extraction with dichloromethane, drying over Na_2SO_4, and evaporation under reduced pressure.

Preparation of the Hydroxy Lactone 2b. (**i**) The 3β-hydroxy-(1′β,2′β-dimethoxycarbonyl)-5α,8α-ethanoergosta-6,22-diene (**4a**; 250 mg, 0.46 mmol) dissolved in dichloromethane (10 mL) containing triethylamine (4 mL) was treated with chlorotrimethylsilane (0.15 mL, 1.2 mmol) for 30 min at 25 °C. After usual workup the mixture afforded the crude 3β-(trimethylsilyl)oxy ester **4b** (265 mg, 0.43 mmol; *Y* = 94%) which was used without purification in the following reaction. A sample, crystallized from acetone, showed mp 144−146 °C. Anal. Calcd for $C_{37}H_{60}O_5Si$: C, 72.50; H, 9.87. Found: C, 72.34; H 9.98.

(**ii**) The crude silyloxy ester **4b** (150 mg, 0.24 mmol) was dissolved in anhydrous diethyl ether (15 mL) and treated with $LiAlH_4$ (30 mg, 0.79 mmol) at reflux for 2 h. At this time, the mixture was cooled, added to ethyl acetate and worked up to afford the 3β-silyloxy diol **4c** (100 mg, 0.18 mmol; *Y* = 75%): mp 183−185 °C (from diisopropyl ether). Anal. Calcd for $C_{35}H_{60}O_3Si$: C, 75.48 ; H, 10.86. Found: C, 75.73; H 11.02.

(**iii**) The 3β-silyloxy diol **4c** (80 mg, 0.14 mmol) was dissolved in benzene and treated with Ag_2CO_3 supported on Celite[13] (2.00 g, 1:1; w/w) at reflux for 12 h. After filtration the solvent was evaporated and the crude product was dissolved in methanol (10 mL) and treated with formic acid (2 mL) at rt for 3 h. Then a saturated solution of $NaHCO_3$ was cautiously added, and the mixture was worked up. The crude product was chromatographed on silica, eluting with hexane−ethyl acetate (100:15, v:v), to afford first the hydroxy lactone **2b** (35 mg, 0.073 mmol; *Y* = 52%): mp 224−225 °C; $[\alpha]^{23}_D$ +8.0 (*c* 1, $CHCl_3$); ^{1}H NMR in Table 2. Anal. Calcd for $C_{32}H_{48}O_3$: C, 79.95; H, 10.06. Found: C, 79.65; H, 10.36. Then the hydroxy lactone **3b** (23 mg, 0.048 mmol; *Y* = 34%) was eluted: 226−228 °C (from diisopropyl ether); all other physicochemical properties were identical in all respect to those described[5] and found by us operating according to the literature.

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(12) Maèk, J. *Org. React.* **1988**, *36*, 249.
(13) Fetizon, M.; Huy, T. H.; Mourgues, P. *Tetrahedron* **1978**, *34*, 209.

Table 2. ^{1}H Assignments of Lactones 2b,e,f

	^{1}H[a]		
proton(s)	lactone **2b** δ (ppm) mult, J (Hz)	lactone **2e** δ (ppm) mult, J (Hz)	lactone **2f** δ (ppm) mult, J (Hz)
3α-H	4.17 dddd, 5.6, 6.3, 11.2, 11,2		
4α-H	2.62 ddd, 2.1,[b] 5.6, 13.3	3.55[c] dd, 2.1, 15.4	absent
4β-H	1.79 dd, 11.2, 13.3	2.67[c] d, 15.4	absent
6-H	5.85 d, 9.1	5.91 d, 9.1	5.91 d, 9.1
7-H	6.14 d, 9.1	6.22 d, 9.1	6.22 d, 9.1
15α-H	overlapped	overlapped	overlapped
18-Me	0.75 s	0.79 s	0.79 s
19-Me	0.91 s	1.08 s	1.08 s
22-H	5.14 dd, 8.4, 15.4	5.14 dd, 8.4, 15.4	5.14 dd, 8.4, 15.4
23-H	5.21 dd, 7.7, 15.4	5.22 dd, 7.7, 15.4	5.22 dd, 7.7, 15.4
1′-H	2.97 d, 10.5	2.70 d, 10.5	absent
2′-H	2.47 ddd, 5.6, 9.1, 10.5	2.52 ddd, 5.6, 9.1, 10.5	2.51 dd, 5.6, 9.1
3′α-H	3.72 dd, 5.6, 9.1	4.13 dd, 5.6, 9.1	4.13 dd, 5.6, 9.1
3′β-H	4.12 dd, 9.1, 9.1	3.74 dd, 9.1, 9.1	3.74 dd, 9.1, 9.1

[a] Chemical shifts taken from the 1D proton spectrum whenever possible: s, singlet; d, doublet; m, multiplet. [b] J long range with the 2α-proton, part of a sterically fixed "W" arrangement of atoms. [c] α and β assignements derived from the relative NOE.

Oxidation of the Hydroxy Lactone 2b. The hydroxy lactone **2b** (150 mg, 0.31 mmol) in acetone (10 mL) was treated with Jones reagent at 0 °C. After evaporation of the solvent, dilution with water, and extraction with dichloromethane, the crude keto lactone **2e** was obtained (140 mg, 0.29 mmol; Y = 93%): mp 228 °C (from diisopropyl ether); $[\alpha]^{23}_D$ +9.8 (c 1, $CHCl_3$); ^{1}H NMR in Table 2. Anal. Calcd for $C_{32}H_{46}O_3$: C, 80.29; H, 9.69. Found: C, 80.04; H, 9.86.

Deuteration of the 3-Keto Lactones 2e and 3e. General Procedure. The same procedure previously used for the deuteration of other keto steroids[7] was used. Each 3-keto lactone **2e** or **3e** (100 mg, 0.21 mmol) was dissolved separately in methanol-*d* (12 mL) containing sodium methoxide (50 mg) and refluxed under nitrogen for 4 h. Then methanol-*d* was removed by distillation and the product taken up in dichloromethane (10 mL) and washed with water. Drying and concentration yielded the appropriate crude pentadeuterated keto lactone (**2f** or **3f**). The keto lactone **3f** (quantitatively obtained from **3e**) showed mp 230−231 °C (from acqueous ethanol); $[\alpha]_D$ = −74.8 (c 1, $CHCl_3$) (lit.[5] −79) and all other physicochemical properties identical to those of the starting ketone **3e**, apart from the mass spectrum and the lack of the signals of 2,2,2′,4,4 protons in the ^{1}H NMR spectrum (Table 1). The keto lactone **2f** (quantitatively obtained from **2e**) showed mp 223−225 °C (from diisopropyl ether) and the ^{1}H NMR spectrum described in Table 2.

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Supporting Information Available: ^{1}H NMR of compounds **2b**, **2e**, **2f**, **3a**, **3b**, **3d**, and **3e**, as well as copies of 2D COSY of compound **3a** (26 pages). This material is contained in libraries on microfiche immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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