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A FACILE TWO-STEP HIGH YIELD APPROACH TO 2-OXASTEROIDS

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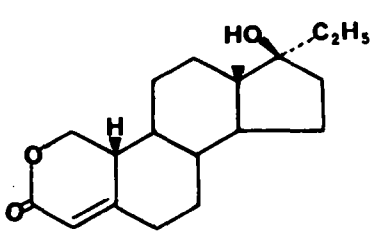
Abstract - The base catalyzed autoxidation of 3-oxo-Δ^4 steroids in aprotic media at circa -25°C occurs nearly exclusively at C_2 of the A-ring, generating rapidly (< 4 hrs) and in high yield the corresponding enol (2-hydroxy-3-oxo-$\Delta^{1,4}$ analog). When the reaction is then allowed to continue at room temperature for several days, the enol is further autoxidized to the related lactol (1-hydroxy-2-oxa-3-oxo-Δ^4 analog) in overall yields generally in the range of 85-95%. Sodium borohydride reduction of the lactol yields the pharmacologically important 2-oxasteroids.

INTRODUCTION

The use of steroidal hormones, such as corticoids, progesterones and various anabolic (muscle building) agents, is well known in modern clinical therapy. However, the beneficial properties of these drugs are often, if not usually, accompanied by unwanted side effects.[1-3] In males taking anabolic hormones, acne, changes in liver function, baldness, testicular atrophy and decreased sperm production have been observed. Many of these muscle building steroids are potent androgens, stimulating in female subjects the development of masculine characteristics: facial hair, male-pattern baldness, deepening of the voice, enlargement of the clitoris and menstrual irregularities. Of particular concern is the observation that most of these changes are <u>not</u> reversible as is commonly believed.

In 1956, the introduction of the 19-norsteroid Nilevar^R (1) proved that the separation of activities is indeed possible.[4] This drug had the desired anabolic property with greatly reduced androgenic side effects when compared to testosterone (2, X = CH_2, R = H) or its 17α-methyl analog (2, X = CH_2, R = CH_3). With the Nilevar^R success as a backdrop and with the emphasis on separation of activities rather than on greater potency, several groups began to study the effect of inserting heteroatoms into the steroidal ring.[2,3]



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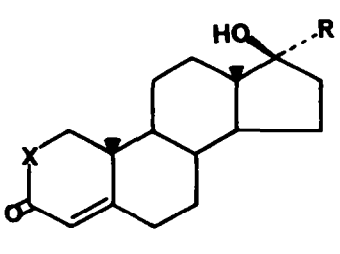

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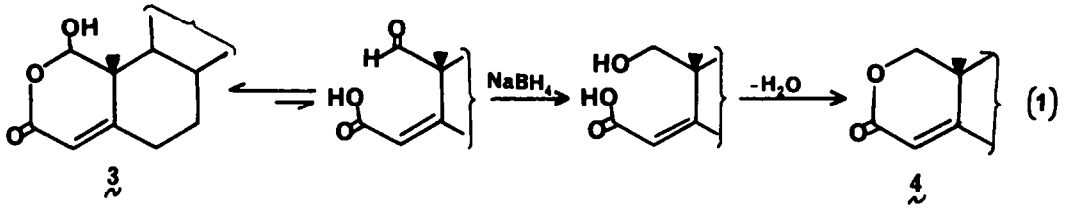
Some success has been observed with 2-oxa-3-oxo-Δ^4 steroids (4; e.g., 2, X = O). Such cyclic α,β-unsaturated lactones are conveniently obtained upon sodium borohydride reduction of the corresponding 1-hydroxy-2-oxa-3-oxo-Δ^4 analogs 3 (equation 1).



3 4 (1)

However, the preparation of Δ^4-lactols 3 is by no means a trivial matter. Indeed many of the approaches reported in the chemical and patent literature are multi-step low yield (< 10%) procedures.[2-14]

RESULTS and PRODUCT CHARACTERIZATION

Scheme 1 outlines the two or three-step high yield approach we have developed for the synthesis of lactones 4, which is based on related work carried out on 2-cyclohexen-1-ones[15-17] (see Discussion). Briefly this procedure utilizes the t-butoxide mediated autoxidation[18] of the parent methylene analog 5 to generate the corresponding lactol 3, which is in turn reduced by $NaBH_4$ to the desired oxasteroid 4. More specifically, the first step involves the in situ generation and oxygenation of the kinetic enolate of 5 in aprotic media (toluene) at -25°C for 1.5-4 hours. The reaction mixture, containing primarily enol 6, is then warmed to room temperature and stirred for another 1-3 days under oxygen during which time further autoxidation produces lactol 3. If desired, the enol can be isolated in yields generally greater than 85% and reacted further as needed. Because the R_f values of a given enone (5) and its corresponding enol (6) and lactol (3) are substantially different from one another, decreasing in the order 5 > 6 > 3, reactions can be conveniently followed and products purified by TLC. Yields of enols and lactols generated by either the direct or two-step approach are given in Table 1.

Table 1: Isolated Yields (and Reaction Times) for the Preparation of Enols 6 and Lactols 3 via the t-Butoxide Catalyzed Autoxidation of Various 3-Oxo-Δ^4 Steroids (5)[a]

	Two-Step Method			Direct Method
Substrate 5	Enol 6	Lactol 3	3 Overall	Lactol 3
3-Cholesten-4-one (5a)	89% (4 hr)	88% (1d)	78%	86% (1d)
Testosterone (5b)	85% (3 hr)	85% (2d)	72%	95% (2d)
Protected Testosterone (5c)	78% (1.5 hr)	34% (3d)	26%	30% (3d)
17α-Methyltestosterone (5d)	91% (4.0 hr)	85% (3d)	77%	85% (3d)
17α-Hydroxprogesterone (5e)	95% (2.5 hr)	89% (7d)[c]	84%	95% (7d)[c]
Progesterone (5f)	60% (1.5 hr)[b]	——[d]	——[d]	——[d]

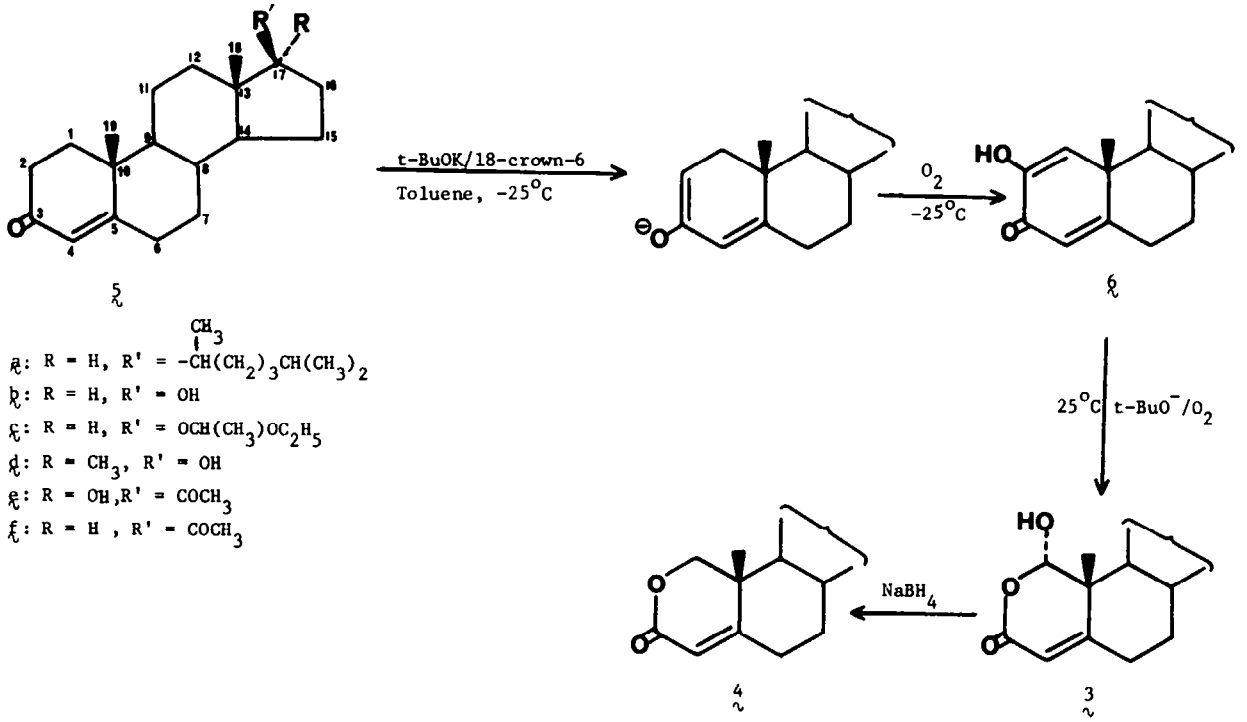
a. Ratio of Substrate: 18-Crown-6: t-BuOK - 1:1.5:3. Substrate concentration ~ 12.5 mM in toluene. Reaction times for lactols are in units of days (d).

b. Varying amounts (up to 20%) of enol 6e were also formed.

c. Reaction carried out at -20°C. Product 3e was accompanied by substantial amounts of unreacted enol. Yield is based on the amount of enol converted.

d. Not investigated; see Results section.

Scheme 1: Synthetic Approach to the Synthesis of 2-Oxa-3-oxo-Δ^4 Steroids



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a: R = H, R' = $-CH(CH_3)(CH_2)_3CH(CH_3)_2$

b: R = H, R' = OH

c: R = H, R' = $OCH(CH_3)OC_2H_5$

d: R = CH_3, R' = OH

e: R = OH, R' = $COCH_3$

f: R = H , R' = $COCH_3$

6

4

3

Table 2. ^{1}H NMR Data[a] for Enols 6

H	6a[b]	6b[c]	6c[d]	6d[e]	6e[f]	6f[g]
1	6.32	6.32(s)	6.32(s)	6.33(s)	6.32(s)	6.32(s)
4	6.17(d,1.5)	6.17(d,1.5[6-ax])	6.16(brs)	6.17(d,1)	6.17(brs)	6.17(brs)
6-ax	2.48(tdd,13,5,1.5)	2.49(tdd,13[6-eq,7-ax]5[7-eq]1.5[4])	2.46	2.49(tdd,13,5,1)	2.50(tdd,14,5.5,1.0)	(g)
6-eq	2.41(ddd,13,5,3)	2.42(ddd,13[6-ax]5[7-ax]3.5[7-eq])	(m,2H)	2.42(ddd,13,5,3)	2.44(ddd,14,5.5,3)	(g)
7-ax	(b)	1.01(dddd,13[6-ax]12.5[7-eq]11.5[8]5[6-eq])	(d)	1.02(qd,12,5)	(f)	(g)
7-eq	1.97(br dq,13,4)	1.97(dddd,12.5[7-ax]5[6-ax]4[8]3.5[6-eq])	(d)	1.99(brd ,12.5,5)	2.0(br dq,14,4)	(g)
11-ax	(b)	1.33(qd,12[11-eq,10,12-ax]6[12-eq]).	(d)	1.33(qd,12,6)	1.61(qd,11,3.5	(g)
16α	(b)	1.47(dddd,14[15β]13[16β]8[17]1.5[15α])	(d)	(e)	(f)	(g)
16β	(b)	2.08(ddd,13[16α]9[17]5.5[15α])	(d)	(e)	2.68(ddd,15[16α]11.5[15α]3[15β])	(g)
17	(b)	3.64(dd,8[16α]9[16β])	3.61(t,7)			(g)
18	0.73(s,3H)	0.82(s,3H)	0.89(s,3H)	0.93(s,3H)	0.79(s,3H)	0.72(s,3H)
19	1.23(s,3H)	1.25(s,3H)	1.27(s,3H)	1.26(s,3H)	1.25(s,3H)	1.27(s,3H)
20	(b)			1.19(s,3H)		
21	0.90(d,7[20]3H)				2.27(s,3H)	2.27(s,3H)
26	0.88 or 0.85					
27	(d,1.5[25]3H)					
OH	6.34(s)	6.34(brs)	(d)	6.41(brs)	6.30(brs)	(g)

(a) 300 MHz unless otherwise indicated. Chemical shift values were determined in $CDCl_3$ and are given in ppm from internal TMS. Coupled hydrogens are indicated within brackets following splitting constants (in Hz).

(b) Multiplets at 2.03 (1H,dt,13,3.5) 2.01-1.90 (1H) 1.90-1.76 (1H) 1.73-1.44 (6H) 1.43-0.88; Lit.[13]: 6.32, 6.18, 1.25, 0.92, 0.82, 0.73.

(c) Assignments and splitting constants were elucidated via double resonance irradiation at 3.64 and 2.45 ppm. Multiplets at 1.91-1.28 (8H) and 1.14-0.88 (2H).

(d) 60 MHz, multiplets at 2.13-1.46 and 1.3-0.90; acetal hydrogen at 4.68 (q, 6).

(e) Multiplets at 1.91-1.54 (10H).

(f) Assignments and splitting constants of protons at 16β and 11-ax were determined from a differential NOE spectrum obtained upon irradiation at 0.79 ppm (18-CH_3). This NOE spectrum also revealed a 2-proton multiplet at 1.52-1.32 (presumably resulting from protons at 8 and 12 eq) and an enhancement of the acetyl methyl resonance at 2.27. Multiplets at 1.88-1.52 and 1.50-0.72.

(g) 60 MHz; multiplets at 2.04-1.4.

Table 3. ^{1}H NMR Data[a] for Lactols 3

H	3a[b]	3b[c]	3c[d]	3d[e]	3e[f]
1	5.48(s)	5.45(d,4[OH])	5.40(s)	5.46(d,4)	5.44(d,4)
4	5.70(d,1.5[6-ax])	5.74(dd,2,0.5)	5.63(s)	5.73(dd,2,0.5)	5.74(dd,2,0.5)
6-ax	2.35(tdd,16.5[6-eq]5.5[7-eq]1.5[4])	2.50-2.30	(d)	2.50-2.30	2.54-2.34
6-eq	2.42(ddd,16.5[6-ax]5[7-ax]3[7-eq])	(m,2H)	(d)	(m,2H)	(m,2H)
16β	(b)	(c)	(d)	(e)	2.69(ddd,15,11.5,3)
17	(b)	3.67(brt,8.5)	3.58(t,7)		
18	0.70(s,3H)	0.79(s,3H)	0.8(s,3H)	0.90(s,3H)	0.76(s,3H)
19	1.20(s,3H)	1.23(s,3H)	1.23(s,3H)	1.22(s,3H)	1.23(s,3H)
20	(b)			1.25(s,3H)	
21	0.90(d,6[20],3H)				2.28(s,3H)
26	0.88 or 0.85				
27	(d,1.5[25],3H)				
OH(C-1)	5.53(brs)	3.60(d,4[1])		3.68(d,4)	3.61(d,4)
OH(C-17)					2.76(brs)

(a) See footnote (a) to Table 2.

(b) Assignments and splitting constants were elucidated via double resonance irradiation at 5.70. Multiplets at 2.00 (d brt,13,3,1H) 1.91-1.73 (2H) 1.71-1.58 (2H) 1.56-1.32 (8H) and 1.17-0.96 (8H). Resonances of minor epimer at 5.33 (H_1) and 1.18 (s,19-CH_3).

(c) Multiplets at 2.15-2.00 (1H) 1.89-1.78 (2H) and 1.69-0.97. Resonances of minor epimer at 5.35 (H_1) and 1.18 (s,19-CH_3).

(d) 60 MHz; 4.68 (q,6, acetal hydrogen); multiplets at 2.53-2.13, 1.91-0.90.

(e) Multiplets at 1.91-1.70 (3H) and 1.69-0.95. Resonances of minor epimer at 5.35 (d,5,H_1) and 1.20 (s,19-CH_3).

(f) Multiplets at 1.93-1.05. Resonances of minor epimer at 5.35 (H_1) and 1.17 (s,19-CH_3).

Table 4. ^{1}H-NMR Data[a] for C-1 Epimers of Lactols 3

H	1	4	19	OH(C-1)	OH(C-17)
3a-α[b]	5.43(d,5)	5.60(dd,2,1.5)	1.22(s,3H)	6.41(d,5)	
3a-β[c]	5.36(d,5.5)	5.63(dd,1.5,1)	1.16(s,3H)	6.47(d,5.5)	
3b-α[d]	5.43(d,5)	5.61(dd,2,1.5)	1.22(s,3H)	6.41(d,5)	3.60(s)
3b-β[e]	5.37(d,5.5)	5.63(dd,1.5,1)	1.17(s,3H)	6.46(d,5.5)	
3d-α[f]	5.44(d,5)	5.61(dd,2,1.5)	1.19(d,0.5,3H)	6.41(d,5)	3.19(s)
3d-β[g]	5.38(d,5.5)	5.63(dd,1.5,1)	1.18(s,3H)	6.46(d,5.5)	3.18(s)
3e-α[h]	5.44(d,4.5)	5.62(dd,2,1.5)	1.22(s,3H)	6.42(d,4.5)	4.27(s)
3e-β[i]	5.40(d,5.5)	5.64(dd,1.5,1)	1.17(s,3H)	6.48(d,5.5)	4.25(s)

(a) See footnote (a) to Table 2 with exception that the solvent is acetone-d_6. α and β refer to orientation of hydroxyl group at C-1. Orientation of major component determined by ^{13}C-NMR analysis; see text. Percentage of each epimeric component is given in footnotes below.

(b) 87%

(c) 13%

(d) 90%

(e) 10%

(f) 89%; assignments were elucidated via double resonance irradiation at 5.61 and 6.41 ppm.

(g) 11%

(h) 87%

(i) 13%

Table 5. ^{1}H-NMR Data[a] for Lactones 4

H	4a[b]	4b[c]	4d[d]
1-eq	4.23(d,11[1-ax])	4.23(d,11)	4.24(d,11)
1-ax	4.00(d,11[1-eq])	4.00(d,11)	4.01(d,11)
4	5.66(t,1.5[6])	5.68(t,1.5)	5.67(t,1.5)
6	2.40-2.30(2H)	2.40-2.33(2H)	2.41-2.33(2H)
17	(b)	3.66(brt,8.5)	
18	0.70(s,3H)	0.79(s,3H)	0.90(s,3H)
19	1.21(s,3H)	1.23(s,3H)	1.24(s,3H)
20	(b)		1.25(s,3H)
21	0.90(d,6[20]3H)		
26	0.87 or 0.85		
27	(d,1.5[25],3H)		
OH(C-17)		2.18(brs)	

(a) See footnote (a) of Table 2.

(b) Assignments of 1-eq and 1-ax were elucidated via double resonance irradiation at 1.21 ppm which resulted in substantial sharpening of the doublet at 4.00 ppm. The 1-ax is in a W-configuration with the C-19 methyl hydrogens. Multiplets at 2.03 (dt,13,3,2H) 1.92-1.76 (3H) 1.71-1.56 (2H) 1.56-0.86. [Lit.[13] 0.7,0.8,0.9, 1.2,3.87-4.33,5.65].

(c) Multiplets at 2.15-2.00 (1H) 1.91-1.81 (2H) 1.71-0.85.

(d) Multiplets at 1.92-1.47, 1.42-0.90.

Table 6. ^{13}C NMR Data[a]

C	6a	6b	6d	6e	3a	3b	3d	3e	4a	4b	4d
1	124.59	124.49	124.47	124.05	100.50	100.62	100.76	100.31	77.09	76.98	76.88
2	146.01	146.08	146.08	146.10							
3	181.58	181.58	181.58	181.46	165.83[b]	165.57[b]	165.88[b]	(b),(c)	168.02	168.00	167.84
4	120.86	121.01	121.00	121.07	112.78[b]	112.83[b]	112.78[b]	112.96[b]	113.38	113.33	113.40
5	173.34	173.00	172.97	172.56	164.90[b]	164.78[b]	165.14[b]	164.87[b]	164.78	164.81[b]	164.70
6	32.98	32.84	32.88	32.85	31.08	30.97	31.06	30.93	30.66	30.60[b]	30.54
7	34.06	33.51	33.66	33.57	30.47	30.05	30.27	30.49	31.14	30.05	30.78
8	35.41	35.49	36.28	35.27	35.00	35.08	35.93	34.92	34.92	34.90	35.74
9	53.62	53.78	53.71	53.05	44.61	44.93	44.90	44.25	49.20	49.23	49.15
10	44.19	44.17	44.17	44.00	42.01	42.06	42.12	41.88	37.87	37.90	37.91
11	23.30	23.57	23.02	22.72	20.82	20.50	20.56	20.39	21.61	21.20	21.25
12	39.54	36.38	38.82	30.01	39.27	36.14	38.44	29.89	39.48	36.09	38.58
13	42.75	43.24	45.76	48.47	42.38	42.80	45.42	47.91	42.29	42.64	45.20
14	55.43	50.13	49.84	49.55	55.50	50.21	49.94	49.78	55.58	50.14	49.85
15	24.41	22.96	23.43	24.12	24.36	23.49	23.43	24.02	24.27	23.36[b]	23.26
16	28.18	30.38	31.41	33.95	28.06	30.05	31.22	33.35	28.00	30.49[b]	31.14
17	56.01	81.44	81.32	89.60	56.17	81.52	81.63	90.01	56.14	81.25	81.31
18	12.05	11.18	14.03	15.48	11.87	10.97	13.87	15.22	11.88	10.98	13.83
19	19.67	19.72	19.73	19.73	17.94	17.99	18.02	17.92	16.43	16.43	16.43
20	35.71		25.85	211.20	35.76		25.67	(c)	35.70		25.77
21	18.58			27.81	18.69			27.72	18.65		
22	36.07				36.15				36.10		
23	23.81				23.87				23.81		
24	39.47				39.52				39.40		
25	27.98				28.01				28.00		
26	22.55				22.56				22.55		
27	22.81				22.82				22.81		

(a) 75.5 MHz ; $CDCl_3$; Values in ppm from internal TMS. Assignments result from analysis of at least one off resonance spectrum, taking into account the correlation between residual coupling and proton chemical shifts.

(b) These signals (within the same column) may be interchanged.

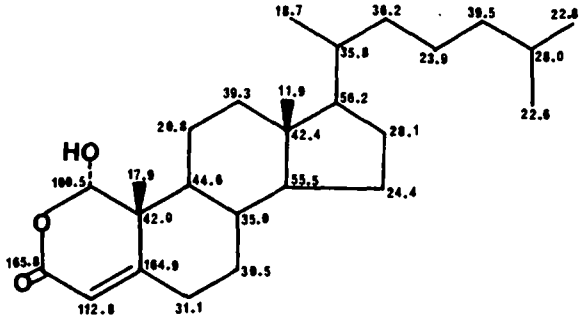
(c) Resonances not detected.

The subsequent reduction of lactols 3 to lactones 4 did not turn out as trivial as we initially thought. The conventional $NaBH_4$ reduction[8] of cholestenone lactol 3a, carried out in aqueous basic methanol, indeed worked well. However, in other systems, a mixture containing large amounts of saturated lactonic products were formed. This problem has already been explored by Pappo[7,12,13,27] who finds that pure lactone can be conveniently prepared by using a two phase system composed of chloroform and an aqueous basic solution of $NaBH_4$. The lactol (aldehydo-acid; see equation 1) is extracted into the aqueous phase and reduced. The resulting lactone is selectively extracted back into the $CHCl_3$ and thereby protected from further reduction. Using this approach 80-90% yields of pure lactone could be obtained.

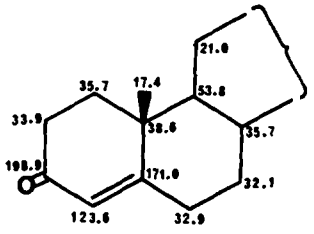
The identity and structure of the various products were elucidated via spectral techniques (PMR, CMR, IR, UV and MS). Tables 2-6 list the ^1H and ^{13}C-NMR resonances for compounds 3, 4 and 6. Enols 6 have typical PMR vinyl absorptions at circa 6.32 and 6.17 ppm (δ) corresponding to H_1 and H_4 respectively. The latter is a doublet (J = 1.5 Hz), with double resonance experiments verifying that it is coupled with the neighboring axial proton at C_6. Lactols 3, on the other hand, show two absorptions at circa 5.73 and 5.45 ppm corresponding to H_4 and H_1 respectively, with H_4 again coupled with H_6-axial. Lactone 4 has a single vinyl absorption at $\sim$ 5.65 ppm and two doublets at $\sim$ 4.2 and 4.0 corresponding to the equatorial (β) and axial (α) protons at C_1.

It should be noted that lactols 3 should in fact exist as two C_1-epimers. Close inspection of the ^1H-NMR spectra of analytical samples of lactols 3 in $CDCl_3$ reveals in all cases additional minor resonances shifted 0.05-0.10 ppm from the major resonances of H_1 and the C_{19}-methyl group. In acetone-d_6 (see Table 4), minor resonances in the area of H_1, H_4, C_{19}-methyl and the C_1-hydroxylic hydrogen could be detected. The similarity in chemical shift, splitting pattern and splitting constant suggest that these minor resonances, representing circa 10% of its mixture, result from the minor epimer.

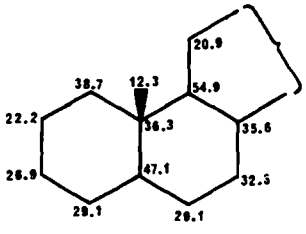
The question of the orientation of the hydroxyl group at C_1 of the major epimer of lactols 3, can be resolved by taking cholest-4-en-3-one (5a) as a model compound for lactol 3a and examining the effect of the introduction of an α- or β-hydroxyl group on the ^{13}C NMR chemical shifts of C_{19}, C_9 and C_{11}. The CMR data[19a] for lactol 3a, cholestane, its 1α and 1β-hydroxylated derivatives and cholestenone 5a are shown below.

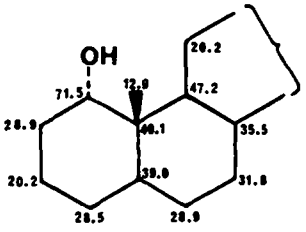


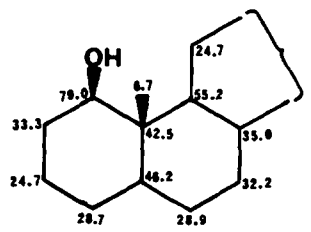
3a



5a







These values indicate that in the cholestane series an α-hydroxy group (axial) shields C_9 by 7.7 ppm, while a β-hydroxy function (equatorial) shields C_{19} by 5.6 ppm. These increases in chemical shift result from the well known γ-effect[19b], in this case from the oxygen. In addition, the β-OH removes the γ-effect from C_1 on C_{11}, thereby deshielding the latter. In the case of lactol 3e, C_{19} and C_{11} are almost invariant relative to the cholestenone model 5e, while C_9 is shielded by 9.2 ppm. This pattern is only consistent with an α-orientation for the OH of the major epimer of 3e.

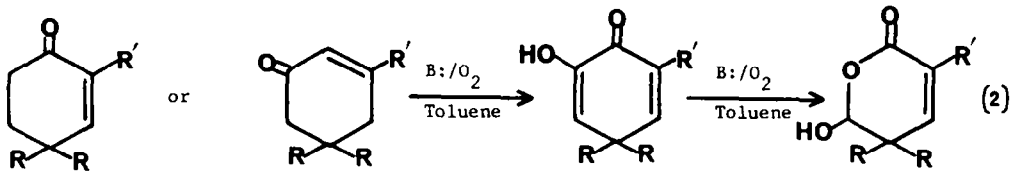
Of the systems investigated, we found the progesterone family experimentally somewhat problematic. Because of the relatively low yield of 6f (at most 60%), we did not pursue its conversion to the corresponding lactol. The low yield of this enol results in part from the concomitant formation of the enol of 17-hydroxyprogesterone (6e). If base catalyzed autoxidation[18] of C_{17} occurs even at -25°, à fortiori that this process should complicate lactol 3f formation at room temperature.

In the case of 17-hydroxyprogesterone (5e), its oxidation to enol 6e proceeded as expected (87% yield in 2 hours). However, the conversion of the latter to lactol proved quite sluggish. To increase the reaction rate, an additional equivalent of t-butoxide was added after two days of reaction. Work-up after one more day gave only a 28% yield of lactol with essentially no recovery of unreacted enol. We discovered, however, that if the reaction is carried out at -20°C and allowed to proceed for 7 days, a 47% yield of lactol could be obtained along with an equivalent amount of unreacted enol. The yields listed in Table 1 for this steroid are based on the amount of converted enol.

Regarding the preparation of lactol 3d by this method, the poor results are somewhat surprising particularly since ketals are presumed to be inert to basic condition. No attempt, however, was made in the present study to optimize yields in this system or to explore the side reactions ocurring.

DISCUSSION

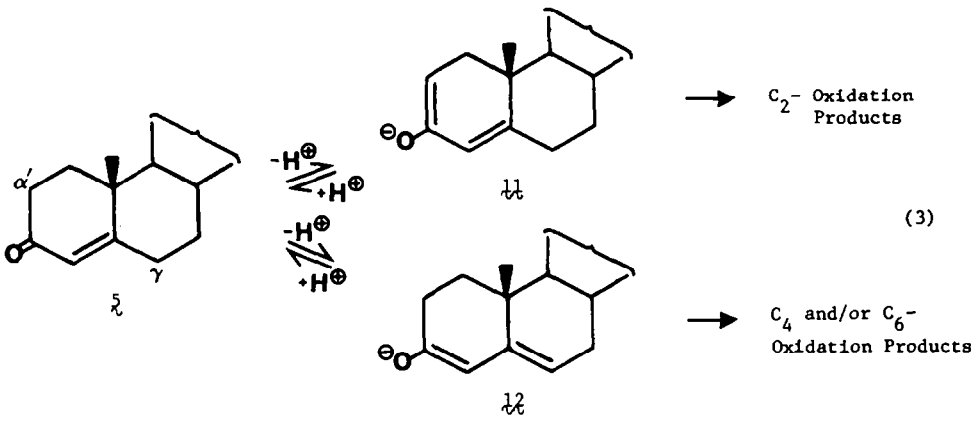
Our recent studies[15,16] on the room temperature base catalyzed autoxidation[18] of 2-cyclohexen-1-ones in aprotic media have indicated that this oxidative process can be used to convert enones 7 or 8 to lactols 10 in an overall yield of 75% and, furthermore, that it proceeds via enols 9, as outlined in equation 2.



7a-c,f 8a,b,d,f 9a-f 10a-e

a: R = CH_3, R' = H
b: R = CH_3, R' = OC_2H_5
c: R = CH_3, R' = OCH_3
d: R = R' = CH_3
e: RR' = $-(CH_2)_5-$, R' = OCH_3
f: R = Ph, R' = H

Initial attempts[17] to extend this approach to steroidal systems proved a bit disappointing, yielding at most only 30% of the desired lactol 3. The reason for the low yield of C_2-oxidation products stems from the possible formation of two dienolates 11 and 12 in the steroidal systems (see equation 3).[20]

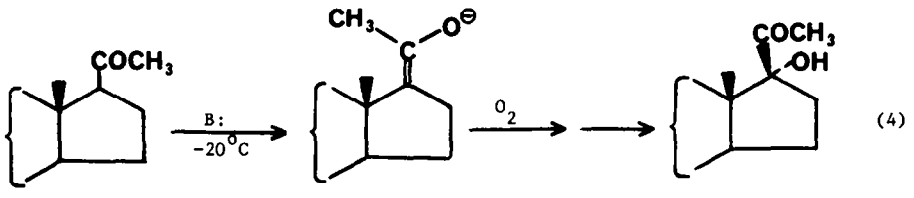


The kinetically favored dienolate 11 results from the abstraction of the more acidic α'-proton from C_2 and leads to C_2 oxidation products (enol 5 and lactol 3). On the other hand, removal of a γ-proton from C_6 generated the thermodynamically favored enolate 12 and ultimately C_4 and/or C_6-oxidation products.

Both aprotic solvents and low reaction temperatures are known to slow the rate of isomerization of 11 into 12. Hence our initial success in isolating even a 30% yield of C_2-products is attributable to the aprotic medium in which these autoxidations were carried out. Indeed, related protic media studies carried out in the early sixties by Camerino and coworkers[21], and more recently by Holland et al.[22], yield only C_4 or C_6-oxidation products. To our pleasant surprise, lowering the reaction temperature to only -20°C was sufficient to slow the isomerization of 11 to 12 to a point where enol 6 could be formed almost exclusively. The latter could be quantitatively converted at room temperature to the desired lactol 3. The results summarized in Table 1 verify the general applicability of this method.

Despite the general success of this approach, two pieces of data in Table 1 require comment. Firstly, the high yield of enol 6c but low yield of the corresponding lactol 3c indicates that the ketal protecting group is not as sturdy as expected. It seemingly cannot withstand the strongly basic conditions of this procedure particularly when the reaction is carried out at room temperature for several days.

The relatively low yield of progesterone enol 6f also underscores a perhaps obvious caveat: in carrying out these reactions one must be cautious about competing or concomitant oxidations at other sites in the molecule. In the case of progesterone, oxidation of the A ring competes with enolate formation and oxygenation at C_{17} of the D ring. This latter process generates the enol of 17-hydroxyprogesterone (5e) as outlined in equation 4.



Indeed, the facile base catalyzed autoxidation of pregnan-20-ones at C_{17} in protic media has been long known and utilized in the synthesis of 17-hydroperoxy and 17-hydroxy derivatives of this family.[23] Interestingly, Gardner et al.[23c] notes in passing that his attempts to obtain 17α-hydroxyprogesterone from progesterone at -20°C in protic solvent were thwarted by what seemed to be, based on U.V. evidence, "at least partial oxidation of the A ring"; no further identification of the product(s) are recorded.

In conclusion, then, the method described herein opens the way for a facile two or three step high yield synthesis of a whole series of 2-oxasteroids. We are presently researching alternative non-basic routes for converting steroidal enols to lactols, with singlet oxygenation thus far offering the greatest promise.[24]

EXPERIMENTAL SECTION

^{1}H NMR spectra were obtained on Varian EM-60 and Bruker AM-300 (Fourier Transform) Spectrometers using TMS as internal standard. In the case of the latter, complex splitting patterns and proton assignments were elucidated by double resonance experiments. The Bruker instrument was also used for ^{13}C NMR using TMS as the internal standard. Infrared absorptions were determined with Perkin Elmer spectrometers models 457 and 621 (asterisked data) while U.V. data were recorded with a Varian DMS 100S U.V.-Visible spectrometer. Mass spectra were run on a GC/MS Finnigan 4000 spectrometer. The fragmentation reported generally results from 70 eV electron impact ionization (EI), with 26 eV EI or 70 eV chemical ionization (CI) runs so indicated. Preparative thin layer chromatography (TLC) was carried out on Merck silica gel F_{254} precoated plates, while analytical runs were performed using Riedel-De Haen DC-microcards SiF. Generally, the eluent was acetone in hexane and the retention times (R_f) recorded below are for the analytical runs. In preparative samples, the bands were scraped from the plates and the product was extracted from the silica by stirring overnight with a CH_3OH-$CHCl_3$ solvent mixture. 18-Crown-6 polyether (Fluka) and potassium t-butoxide (Fluka) were used as supplied and stored in a desiccator. Methyl iodide was distilled and stored under argon at -10°C. The steroids 5a, b, d and f were all commercially available from Aldrich. 5e was obtained from Makor Chemicals (Jerusalem) while 5c was prepared as described below. Melting points are uncorrected.

Preparation of 17β-(1'-Ethoxyethoxy)-4-androsten-3-one (5c) - The hydroxy group of testosterone was protected with ethyl vinyl ether according to the general procedure of N. Miyashita et al.[25] The product was chromatographed on silica using 20% acetone as eluent and identified by its spectral data.

5c: MP (from column) 70-74°; R_f = 0.38; ^{1}H NMR ($CDCl_3$) δ 5.66 (s, 1H, H_4) 4.66 (q, J = 8 Hz, 1H, acetal H) 3.53 (t, J = 7Hz, 1H, H_{17}) 2.26 (m) 2.00-1.4 (m) 1.3 (br s) 1.2 (br s, C_{19}-methyl) 0.8 (s, C_{18}-methyl); MS (70 eV, CI) 361 (M^+ + 1) 288 (M^+ + 1 - $CH(CH_3)OC_2H_5$).

General Procedure for the Preparation of 2-Hydroxy-3-oxo-$\Delta^{1,4}$ Steroids (Enols 6). Steroid 5 and crown ether in a molar ratio of 1:1.5 were dissolved in sodium dried toluene (80-100 ml per mmol of steroid). The reaction vessel was cooled to -27±3° in a dry-ice/acetone bath and 3 mole equivalents of potassium t-butoxide were added. The vessel was then capped with a rubber septum and connected via a syringe needle to an oxygen filled balloon. The reaction mixture was magnetically stirred under oxygen until TLC showed the essentially complete disappearance of substrate (ca. 1.5-4 hours, see Table 1). The oxygen balloon was then removed, the reaction mixture was allowed to warm to room temperature and neutralized with 10% HCl. The toluene layer, diluted with equal amount of ether, was washed thrice with 10% $NaHCO_3$ solution to remove inorganic salts, crown ether, t-butanol and any organic acids. The organic layer was dried over $MgSO_4$ and evaporated to dryness yielding the desired enol 6. The latter was purified further by recrystallization or preparative TLC (25% acetone in hexane). Yields and reaction times are given in Table 1. ^{1}H-NMR and ^{13}C-NMR data are given in Tables 2 and 6.

6a: MP (98% CH_3OH -2% H_2O) 108°C [Lit[13]: 106.5-107.5] R_f = 0.61; IR* ($CHCl_3$) 3500 (br, m, OH) 1640 (s, C=O) 1610 (w, C=C) cm^{-1} [Lit[13]: 3448, 1639]; UV (CH_3OH) λ_{max} 254 (ε 13,900) [Lit[13]: λ_{max} 255 (ε 14,800)]; MS (28 eV) m/e 398 (M^+, 10.87 %) 383 (M^+ - CH_3, 1.89%) 356 (M^+ - CH_2=$CH(CH_3)$, < 0.5%) 313 (M^+ - C_6H_{13}, 1.70%) 285 (M^+ - C_8H_{17}, 31.68%) 150 (49.16%) 137 (100%); Anal.: calc. ($C_{27}H_{42}O_2$): C 81.35%, H 10.62%, O 8.03%; found C 81.37, H 10.46, O 7.90.

6b: MP (acetone-hexane) 204-205°C [Lit[26]: 207-209]; R_f = 0.16; IR* ($CHCl_3$) 3420 (br, m, OH) 1635 (s, C=O) 1610 (w, C=C) cm^{-1} [Lit[26]: 3484, 3344, 1634]; UV (CH_3OH) λ_{max} 254 (ε 11,400) [Lit[26]: λ_{max} 254 (ε 15,400)]; MS (26 eV) m/e 302 (M^+; 9.58%) 284 ($M^+ - H_2O$, 3.72%) 269 ($M^+ - H_2O - CH_3$, 1.60%) 150 (20.61%) 147 (58.82%) 137 (100%); Anal.: calc. ($C_{19}H_{26}O_3$) C 75.46%, H 8.67%, O 15.87%; found C 75.63, H 8.72, O 15.71.

6c: R_f = 0.31 (20% acetone in hexane); MS (CI) m/e 375 ($M^+ + 1$) 303 ($M^+ + 1 - CH(CH_3)OC_3H_5$).

6d: MP (acetone-hexane) 175-176.5°C [Lit[26]: 178-180°]; R_f = 0.213; IR ($CHCl_3$) 3610 (w, OH) 3450 (m, br, OH) 1635 (br, s, C=O) 1605 (w, C=C) cm^{-1}; UV (CH_3OH) λ_{max} 254 (ε 17,230) [Lit[26]: λ_{max} 254 (ε 14,300); MS (26 eV) m/e 316 (M^+, 6.56%) 298 ($M^+ - H_2O$, 3.22%) 283 ($M^+ - H_2O - CH_3$, 5.55%) 161 (44.17%) 150 (30.00%) 137 (100%); Anal: calc. ($C_{20}H_{28}O_3$) C 75.91, H 8.92, O 15.17; found 76.06, H 8.95, O 15.04.

6e: MP (acetone-hexane) 212-214°; R_f = 0.18; IR (acetone) 3500 (br, s, OH) 1635 (br, s, C=O) cm^{-1}; UV (CH_3OH) λ_{max} 253 (ε 14,550); MS (26 eV) m/e 344 (M^+, 0.5%) 301 ($M^+ - CH_3CO$, 4.23%) 283 ($M^+ - CH_3CO-H_2O$, 3.20%) 163 (11.64%) 147 (13.67%) 137 (100%); Anal. calc. ($C_{21}H_{28}O_4$) C 73.23, H 8.19, O 18.58; found C 72.77, H 8.35, O 18.92.

6f: MS (70 eV) m/e 328 (M^+) 300 ($M^+ - CO$) 285 ($M^+ - CH_3CO$) 282 ($M^+ - CO-H_2O$).

General Procedure for the Preparation of 1-Hydroxy-2-oxa-3-oxo-Δ^4 Steroids (Lactols **3**). Enol **6** (isolated as above), crown ether and potassium t-butoxide in a molar ratio of 1:1.5:3 were dissolved in sodium dried toluene (~ 90 ml per mmole of enol). The reaction vessel was capped with a rubber septum and connected via a syringe needle to an oxygen filled balloon. The reaction was magnetically stirred at room temperature until TLC showed the essentially complete disappearance of starting material (generally 1-3 days, see Table 1). In the case of 17-hydroxyprogesterone (**5e**) the conversion of enol **6e** to lactol **3e** was carried out at -20°C (cold room) for 7 days.

Reactions were quenched by neutralization with 10% HCl. The toluene layer was diluted with an equal amount of ether and the organic phase was washed thrice with 10% $NaHCO_3$ solution. [Generally speaking, lactols **3** do not pass into the aqueous phase during the bicarbonate extractions, but there are exceptions as in the case of lactols **3b** and **3e**. In such instances, the aqueous extracts are acidified with concentrated HCl and extracted thrice with ether. If any lactol remains in the above organic phase the organic extracts are combined with it]. The ether solution is dried over $MgSO_4$ and evaporated to dryness. Products were purified by recrystallization or preparative TLC (1:1 acetone-hexane). ^1H and ^{13}C-NMR spectral data are given in Tables 3, 4 and 6.

Alternatively, lactol **3** can be prepared directly from steroid **5**. The steroid is oxidized for 1.5-4 hours at -25°C as described in the previous section. The reaction mixture containing primarily enol is then allowed to warm to room temperature and continue stirring at room temperature until enol **6** is converted to product(s). The workup procedure is the same as described above. In the case of 17-hydroxyprogesterone (**5e**) the reaction mixture was not warmed to room temperature but was rather allowed to continue reacting for one week at -20°C (cold room) yielding 33% lactol and twice as much enol. Yields and reaction times for the various methods are given in Table 1. The yields of lactol **3e** are calculated based on converted enol, assuming in the direct method that the starting steroid is completely converted to enol.

3a: MP (pet. ether-acetone) 137.5-138.5°C; R_f = 0.64; IR* ($CHCl_3$) 3575 (w, OH) 3320 (br, m, OH) 1720, 1690 (s, C=O) 1640 (w, C=C) cm^{-1}, UV (CH_3OH) λ_{max} 227 (ε 14,100); MS (CI) m/e 403 ($M^+ + 1$); MS (26 eV) m/e 402 (M^+, 0.05%) 384 ($M^+ - H_2O$, 0.5%) 369 ($M^+ - H_2O - CH_3$, 0.73%) 356 ($M^+ - HC(OH)O$, 100%) 341 ($M^+ - HC(OH)O - CH_3$, 12.8%) 328 ($M^+ - HC(OH)OCO$, 1.81%) 314 ($M^+ - HC(OH)OCO - HC(CH_3)CH_2$, 6.1%); Anal.: calc. ($C_{26}H_{42}O_3$): C 77.46, H 10.51 O 11.92; found C 77.47, H 10.57, O 12.04.

3b: MP (acetone-hexane) 248° [Lit[9]: 244-245°]; R_f = 0.23; IR ($CHCl_3$) 3315 (br, m, OH) 1718, 1680 (s, C=O) 1635 (w, C=C) cm^{-1} [Lit[9]: 1718]; UV (CH_3OH) λ_{max} 226 (ε 13,900)]; MS (CI) m/e 307 ($M^+ + 1$); MS (26 eV) m/e 260 ($M^+ - HC(OH)O$, 100%) 245 ($M^+ - CO_2-OH$, 3.3 64%) 227 ($M^+ - CO_2-OH-H_2O$, 1.88%)

218 (14.47%); Anal.: calc. ($C_{18}H_{26}O_4$) C 70.56, H 8.36, O 20.70; found C 70.12, H 8.36, O 20.70.

3c: R_f = 0.125 (20% acetone in hexane); MS (70 eV) m/e 378 (M^+) 306 (M^+ - $CH(CH_3)OC_2H_5$) 278 (M^+ - $CH(CH_3)OC_2H_5$-CO).

3d: MP (acetone-hexane) 247°-254°C [Lit[7]: 250-265°]; R_f = 0.28; IR ($CHCl_3$) 3300 (br, m, OH) 1715, 1692 (s, C=O) 1640 (w, C=C) [Lit[7]: 3509, 3278, 1709, 1631]; UV (CH_3OH) λ_{max} 226 [ε 13,700] [Lit[7]: 226 (14,200)]; MS (26 eV) m/e 320 (M^+, 0.65%) 274 (M^+ - HC(OH)O, 44.8%) 259 (M^+ - CH(OH)O-CH_3, 1.25%) 174 (15.99%) 124 (20.77%) 71 (100%); Anal.: calc. ($C_{19}H_{28}O_4$) C 71.22, H 8.81, O 19.97; found C 71.08, H 8.91, O 19.90.

3e: MP (acetone-hexane) 215-225°C; R_f = 0.29; IR ($CHCl_3$) 3665 and 3580 (m, OH) 1720, 1680 (s, C=O) 1640 (w, C=C) cm^{-1}; UV (CH_3OH) λ_{max} 226 (ε 13,000); MS (70 eV) m/e 348 (M^+, 14.28%) 330 (M^+ - H_2O, 3.57%) 320 (M^+ - CO, 2.67%) 305 (M^+ - CH_3CO, 39.70%) 302 (M^+ - CH(OH)O, 21.83%) 287 (M^+ - CH(OH)O-CH_3, 100%).

General Procedure for the Preparation of 2-Oxa-3-oxo-Δ^4 Steroids (Lactone 4) - To a solution of 1.55 mmole of lactol 3 in 230 ml of $CHCl_3$ is added successively a solution of 0.5 g $NaBH_4$ (13.2 mmole) in 70 ml of H_2O and 0.5 ml of 10% aqueous NaOH. The mixture was vigorously stirred at ambient temperature for 5 hours. The organic phase was separated from the aqueous layer, then washed successively with aqueous NaOH and water, and dried over $MgSO_4$. The solvent was removed and the product recrystallized. A small portion of the aforementioned aqueous layer of the reaction mixture was acidified with 10% HCl and extracted with $CHCl_3$. Should TLC indicate that substantial amounts of lactol remain unreacted, another 230 ml of $CHCl_3$ is added and the reaction is allowed to continue overnight to completion. The organic phase is then treated as above. Isolated yields of lactone range from 80-90%. TLC retention times were determined in 1:1 acetone-hexane. Compounds 4a[13], b[7,12] and d[7,12] are known. NMR data are given in Tables 5 and 6.

4a: MP (acetone-hexane) 125-126°C [Lit[13]: 126-127°]; R_f = 0.82; IR ($CHCl_3$) 1715, 1690 (s, C=O) 1625 (w, C=C) [Lit[13]: 1724, 1631] cm^{-1}; MS (70 eV) m/e 386 (M^+, 29.30%) 342 (M^+ - CO_2, 11.87%) 341 (M^+ - HCO_2, 83.77%) 273 (M^+ - C_8H_{17}, 30.39%) 261 (M^+ - C_9H_{17}, 32.30%) 247 (9.20%) 201 (12.47%) 187 (31.43%) 147 (40.36%) 126 (100%); UV (CH_3OH) λ_{max} 224.7 (ε 12,000).

4b: MP (acetone-hexane) 201-202°C [Lit[7,12]: 205-207°]; R_f = 0.5; IR ($CHCl_3$) 3420 (br, w, OH) 1710 1690 (s, C=O) 1625 (w, C=C) [Lit[7]: 1724, 1700, 1628] cm^{-1}; MS (70 eV) 290 (M^+, 25.37%) 272 (M^+ - H_2O, 15.59%) 246 (M^+ - CO_2, 29.12%) 245 (M^+ HCO_2, 33.67%) 228 (M^+ - H_2O-CO_2, 12.17%) 227 (M^+ - H_2O-HCO_2, 16.84%) 203 (M^+ - H_2O-HCO_2-CH_3, 15.36%) 201 (M^+-H_2O-HCO_2-OH, 15.02%) 147 (81.11%) 126.18 (100%); UV (CH_3OH) λ_{max} 223.7 (ε 14,500) [Lit[7]: 223.5 (14,500)].

4d: MP (acetone-hexane) 223-231°C [Lit[7,12]: 230-240°(dec.)]; R_f =0.58; IR ($CHCl_3$) 3440 (br, m, OH) 1715, 1688 (C=O, s) 1628 (w, C=C) [Lit[7]: 3636, 1730, 1709, 1631) cm^{-1}; MS (70 eV) m/e 304 (M^+, 100%) 286 (M^+ - H_2O, 7.44%) 271 (M^+ - H_2O-CH_3, 18.17%) 247 (M^+ - CHO_2C, 76.10%) 241 (M^+ - H_2O-HCO_2, 12.80%) 234 (11.34%) 231 (M^+ - CH_3-CH_2O_2C, 31.10%) 201 (17.80%) 187 (15%); UV (CH_3OH) λ_{max} 223.4 (ε 13,960) [Lit[7,12]: 223.5 (12,500)].

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