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The Photosensitized Oxidation of α-Keto Enols: A Singlet Oxygen Approach to 2-Oxasteroids

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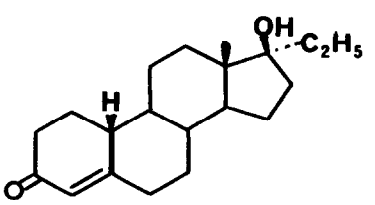
Abstract: Fluoride ion catalyzed photosensitized singlet oxygenation of 2-hydroxycyclohexa-2,5-dien-1-ones **15a** and **b** and the related steroidal α-keto enols **18a-g**, generated the cyclohexenone lactols **16a-b** and the corresponding steroidal analogs **19a-g** generally in moderate to good yields (60-75%). Since the lactols can be conveniently reduced to the desired 2-oxasteroids in high yields, this $^1O_2$ route presents itself as a synthetically acceptable alternative to the previously reported BCA approach[3a] for the preparation of 2-oxasteroids, especially in the case of base sensitive compounds.

The beneficial properties of steroidal hormones is often accompanied by unwanted side effects.[1] For example, use of the well known anabolic male hormone testosterone or its derivatives for the development of muscle tissue in female patients commonly results in the appearance of secondary male sex characteristics. The introduction of the 19-nor-steroid Nilevar^R (17β-hydroxy-19-norpregn-4-en-3-one, **1**) in 1956 by Searle proved that separation of the activities was indeed possible.[2] Several research groups then explored the effect of inserting atoms other than carbon into the ring system of steroidal hormones. Although the activity of the heteroatomic 4-oxa-3-oxosteroids proved disappointing, the corresponding 2-oxa systems showed promise. Indeed, in 1964 Searle introduced the 2-oxasteroid Anavar^R (17β-hydroxy-17-methyl-2-oxa-5α-androstan-3-one, **2**), a valuable anabolic agent almost devoid of androgenic side-effects.[1b]



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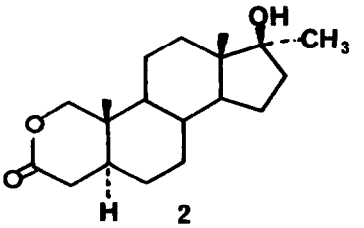

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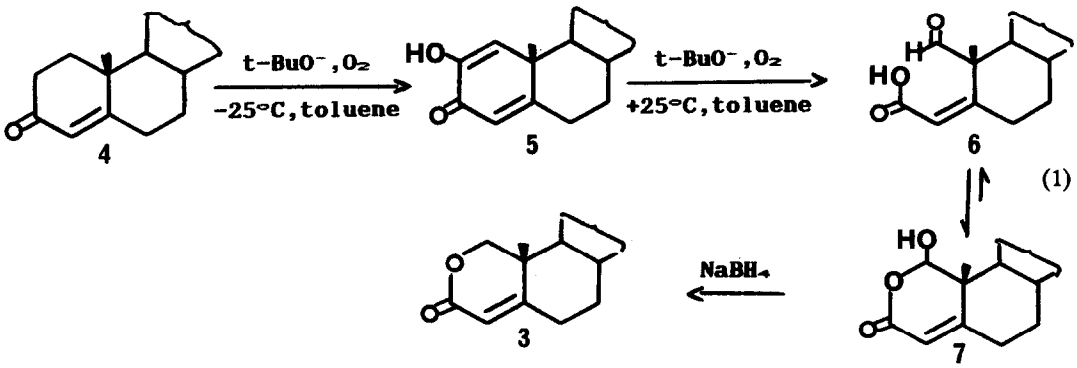
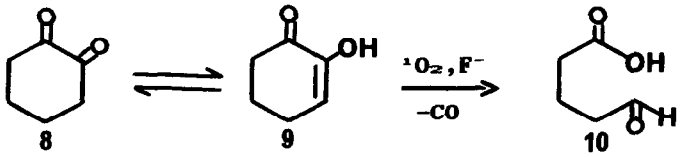
The preparation of the related 2-oxa-3-oxo-Δ^4 systems (**3**) had, until recently, proven quite problematic, primarily because the synthetic approaches employed were generally multi-step low-yield processes.[1b,3] In 1986, we reported a facile, two-step, high yield approach to steroidal lactones **3** (equation 1).[3] In the first step, the kinetically controlled (-25 ^{o}C, aprotic media) base catalyzed autoxidation (BCA) of the corresponding homoatomic parent enone **4** results in the rapid (<4 h) formation of keto enol **5**. The latter is slowly (1-3 days) oxidized further at room temperature to aldehydo acid **6** which spontaneously cyclizes generating lactol **7**.[4] Sodium borohydride reduction of the lactol yields the desired lactone, 2-oxasteroid **3**. This approach has been applied to various steroidal systems[3] and has been shown to be quite general in nature.



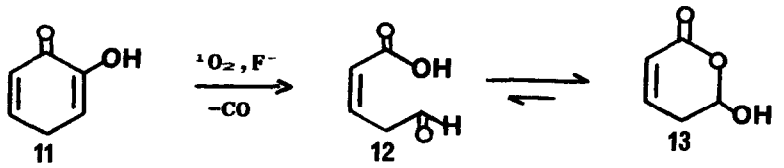
Considering the extremely basic conditions required, it should be obvious that the applicability of this approach will depend on whether other base sensitive substituents or moieties are present on the steroidal ring system. Indeed, we found that progesterone could be converted to the corresponding enol in moderate yield (60%), but that oxidation at C-17 of the D-ring competed effectively with any further BCA of the enol to lactol.[3] Clearly, alternate synthetic routes to 2-oxasteroids were called for, and our attention was drawn to possible singlet molecular oxygen ($^1O_2$) approaches.

Wasserman and Pickett[5] have recently reported that fluoride ion efficiently catalyzes the singlet oxygen ene-type reaction of enols and enolates[4] and, furthermore, that α-keto enols **9** (or the tautomeric α-diketones **8**) can be photooxidatively converted to the corresponding aldehydo carboxylic acids **10** (equation 2).



(2)

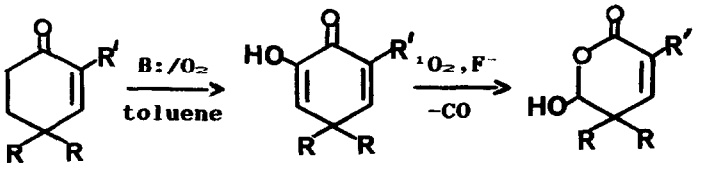
No work has been reported on the corresponding unsaturated systems **11**. However, our own preliminary studies on such systems suggested that here, too, the reaction should proceed well to yield the corresponding aldehydo acids (**12**, equation 3). Because of the presence of the cis enone double bond, which forces the acid and aldehyde moieties into close proximity of one another, these aldehydo acids are expected to cyclize spontaneously to the desired lactols **13**. We, therefore, decided to investigate the applicability of this approach to the synthesis of 2-oxasteroids.



(3)

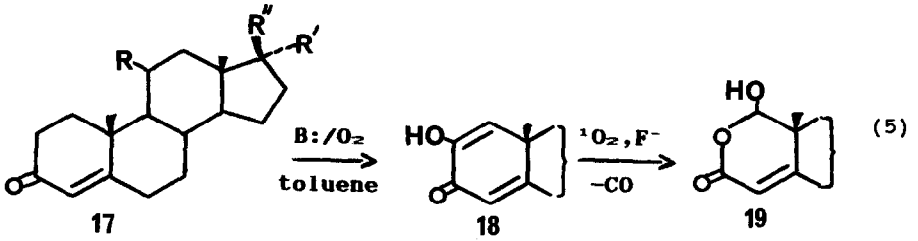
RESULTS AND DISCUSSION

For the purpose of this study, 2-hydroxycyclohexa-2,5-dien-1-ones **15a**[6] and **15b**[6] and the related steroidal enols **18a-g**[3,7,8,9] were prepared via the superoxide or low temperature t-butoxide mediated base catalyzed autoxidation (BCA) of the corresponding conjugated enones in aprotic media (equations 4 and 5, respectively).



(4)

a: R = CH_3, R' = OC_2H_5 b: R = Ph, R' = H



(5)

a: R=R'=H;
R"=CH(CH$_3$)(CH$_2$)$_3$CH(CH$_3$)$_2$

b: R=R'=H; R"=OH

c: R=H; R'=CH$_3$; R"=OH

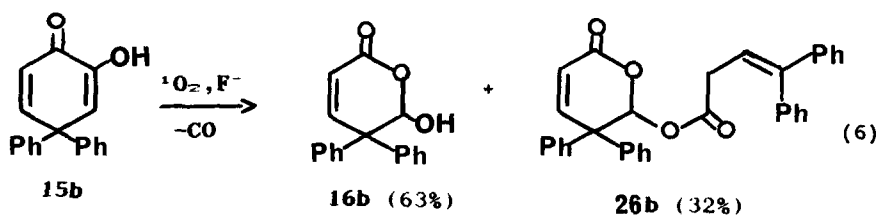
d: R=H; R'=OH; R"=COCH$_3$

e: R=R'=H; R"=COCH$_3$

f: R==O; R', R"=BMD

g: R=H; R', R"=BMD

Fluoride ion catalyzed photosensitized oxidation of α-keto enols **15a,b** and **18a-g**, following the Wasserman and Pickett procedure[5,10,11], indeed generated the desired lactols (equations 4 and 5). In the case of **15b**, in addition to lactol **16b**, lactol ester **26** was also formed (equation 6).



15b **16b** (63%) **26b** (32%)

(6)

The identity of the lactols was confirmed by comparing their spectral data with authentic samples independently synthesized by base catalyzed autoxidation.[3,6e] Assignments in the case of lactol ester **26** were based upon a comparison of its spectral data with those of lactol **15b** and of methyl 4,4-diphenylbut-3-enoate[12] and were confirmed by two-dimensional carbon-proton correlation experiments optimized for one-bond and long range interactions, respectively.

The isolated yields, outlined in Table I, were low in the case of **15a** and moderate in the case of **15b** (29 and 63%, respectively), but good (generally above 70%) in the case of the steroidal analogs **18a-g**. As with the previously studied steroidal lactols **19a-d**,[3] **19e** is formed as an epimeric mixture, with the C-1 hydroxyl group oriented preferentially α (α:β ≈ 9:1). Interestingly, however, in **19f** and **19g**, the α-epimer seems to predominate almost exclusively.

Table I: Isolated lactol yields in the fluoride mediated photooxidation of α-keto enols **15a-b** and **18a-g** as compared to the BCA approach.

Enol	(Parent Enone)	Irradiation Time (h)	Lactol	Yield $^1O_2$	Yield BCA
15a		4.0	**16a**	29%	80%[a]
15b		9.5	**16b**	63%[b]	0%[a]
18a	(Cholest-4-en-3-one)	7.0	**19a**	73%	88%[c]
18b	(Testosterone)	4.5	**19b**	71%	85%[c]
18c	(17α-Methyltestosterone)	5.5	**19c**	72%	85%[c]
18d	(17α-Hydroxyprogesterone)	3.0	**19d**	72%	89%[c]
18e	(Progesterone)	7.0	**19e**	61%	0%[c]
18f	(Cortisone-BMD)	6.0	**19f**	75%	---
18g	(Cortexolone-BMD)	3.0	**19g**	72%	80%[d]

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a. Data taken from reference 6e.

b. A 32% yield of lactol phenylcinnamate **26** was also obtained.

c. Data taken from reference 3.

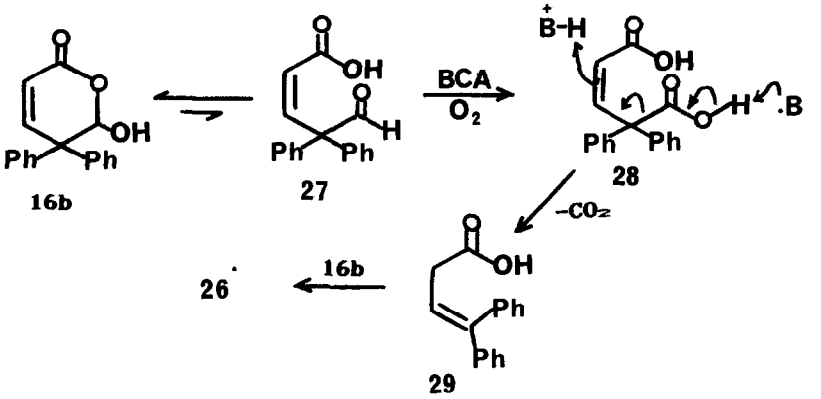
d. From this work.

Several observations are relevant at this juncture. Firstly, as can be seen from Table I, lactol yields from the photosensitized oxidation of enols are generally a bit lower than those obtained via BCA.[3,6d] Nevertheless, for base sensitive substrates, the $^1O_2$ route to 2-oxasteroids is truly a synthetically viable alternative to the previously published[3] BCA approach. Indeed, included in the successes of Table I are gem-diphenyl lactol **16b**[6e] and progesterone lactol **19e**[3] which could not be prepared by BCA.

This brings us to our second point. The successful singlet oxygenation of **15b** is, in fact, somewhat surprising. The resistance of this enol to BCA had been rationalized on the grounds that the gem-diphenyl group at C-4 sterically blocks triplet molecular oxygen approach to C-3, the terminal carbon of the enolate system.[6e] It is not obvious why singlet oxygenation, well known for its steric sensitivity,[13] should not suffer similar inhibition with this enolate. The answer probably lies in the differing transition states involved in these processes. Triplet oxygenation of an enolate requires free access to the p-orbital at C-3, which is presumably precluded in the enolate of **15b**. In contradistinction, the related singlet

oxygen approach is expected to be less congested, involving initial interaction at the center of the enol double bond, as suggested by Stephenson and Frimer[13b,14] for other $^1O_2$ ene processes.

We close by commenting on the formation (in a 32% isolated yield) of lactol ester **26** in the fluoride catalyzed photooxidation of enol **15b.** As outlined in equation 7, we propose that **26** simply results from the esterification of 4,4-diphenylbut-3-enoic acid **29** by lactol **16b.** The 3-butenoic acid **29** is generated, in turn, via the facile autoxidation of the open aldehydo acid form (**27**) of lactol **16b,** which initially produces diacid **28** and subsequently, upon facile decarboxylation, monoacid **29.**



(7)

Indeed, when a chloroform solution containing tetramethylammonium fluoride and pure lactol **16b** was allowed to stir overnight in an oxygen atmosphere, TLC indicated that a major portion of the lactol had been converted to lactol ester **26.** The conversion is essentially complete and quantitative after 3 days. This autoxidative process seems to be a fluoride-mediated BCA, since an attempt to repeat this oxygenation reaction in the absence of base leaves the lactol virtually unchanged.

The basic fluoride ion presumably mediates the subsequent decarboxylation step as well. As noted in a previous study on the BCA of 6,6-diphenylcyclohex-2-en-1-one[6d] where diacid **28** is also the putative intermediate, the latter should be particularly prone to decarboxylation since it is doubly activated by the adjacent gem diphenyl group and the β,γ-double bond.

In summary, then, we have demonstrated that the singlet oxygenation of 2-hydroxy-3-oxo-$\Delta^{1,4}$ steroids produces the corresponding lactols in moderate (70-75%) yields. The latter in turn, can be conveniently reduced to the desired 2-oxasteroids in high yields.[3] Hence, this $^1O_2$ route presents itself as a synthetically acceptable alternative to the previously reported[3] BCA approach for the preparation of 2-oxasteroids, especially for base sensitive compounds. We are presently exploring further application of these routes for the synthesis of 2-aza and 2-thiosteroids.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were obtained on a Bruker AM 300 Fourier transform spectrometer. Assignments were facilitated by correlating proton and carbon chemical shifts through analysis of residual couplings in off-resonance decoupled spectra. In all cases, TMS served as the internal standard. IR spectrometers used were generally Perkin Elmer models 457 and 621, though spectra designated "FTIR" were taken with the Nicolet 60 SXB FTIR. UV-Visible absorptions were determined with a Varian DMS-100 spectrometer. Mass spectra were run on a Finnigan-4000 GC/MS machine. 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 microcards. The retention times given are for the analytical runs, with the eluting solvent 25% acetone in hexane unless specified otherwise. Potassium t-butoxide (Fluka) was ground into a fine powder in a glove bag under dry argon prior to use. 18-Crown-6 polyether (Fluka) was used as supplied if dry and crystalline, otherwise it was recrystallized from acetonitrile)[15] and stored along with the above potassium t-butoxide in a desiccator. Cortisone, cortisone acetate, cortexolone and adrenosterone are all commercially available (Aldrich) and were used as supplied.

Preparation of enols 15 and 18: Enols **15a-b**[6] and **18a-e**[3] were synthesized by published procedures. The previously described[3] low temperature (-30 ± 5 ^oC) t-butoxide mediated BCA of cortisone-BMD[7a] and cortexolone-BMD[7b] yielded enols **18f** (reaction time: 3 h; 74% yield) and **18g** (reaction time: 1.5 h; 95% yield) respectively. The complete spectral data of **18e-g** are cited below.

18e: mp (acetone-hexane) 184-187 ^oC [Lit.[16] 189-190^0]; R_f 0.27; ^1H NMR ($CDCl_3$) δ 6.38 (s, 1H, OH), 6.32 (s, 1H, H_1), 6.18 (d, $J_{4,6ax}$=1.0 Hz, 1H, H_4), 2.53 (br t, J=6 Hz, 1H, H_{17}), 2.47-2.40, 2.26-1.84 and 1.88-1.00 (overlapping m), 2.12 (s, 3H, C_{21} methyl), 1.24 (s, 3H, C_{19} methyl), 0.69 (s, 3H, C_{18} methyl); ^{13}C NMR ($CDCl_3$) δ 208.94 (C_{20}), 181.54 (C_3), 172.76 (C_5), 146.18 (C_2), 124.21 (C_1), 121.08 (C_4), 63.38 (C_{17}), 55.65 (C_{14}), 53.52 (C_9), 44.19 (C_{13}), 44.06 (C_{10}), 38.62 (C_{12}), 35.42 (C_8), 33.90 (C_7), 32.84 (C_6), 31.35 (C_{21}), 24.59 (C_{15}), 23.29 (C_{16}), 22.94 (C_{11}), 19.70 (C_{19}), 13.42 (C_{18}); IR ($CDCl_3$) 3420 (br,m,O-H), 1700 and 1640 (s,CO), 1600 (w,C=C) cm^{-1}; MS (EI, 55 ev), m/e 328 (M^+, 21%), 310 (M-H_2O, 1.6%), 300 (M-CO, 0.3%), 286 (M-CH_2CO, 3%), 285 (M-CH_3CO, 2.5%), 191 (M-$C_8H_9O_2$ [A-ring + CH_3 + CH_2], 12%), 177 (M-$C_8H_9O_2$-CH_2, 6%), 150 (M-$C_8H_9O_2$-C_3H_5, 19%), 149 (M-$C_8H_9O_2$-$COCH_2$, 7%), 137 ($C_8H_9O_2$, 100%), 122 ($C_8H_9O_2$-CH_3, 2%), ; UV (CH_3OH) λ_{max} (ϵ_{max})= 253.4 (16020) nm [Lit.[16] 253.5 (14500)].

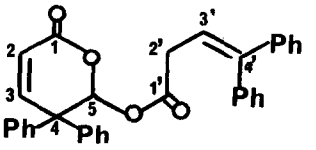
18f: mp (from column) 231-235 ^oC; R_f 0.21; ^1H NMR ($CDCl_3$) δ 6.98 (s, 1H, OH), 6.26 (s, 1H, H_1), 6.19 (d, $J_{4,6ax}$=1.0 Hz, 1H, H_4), 5.21 (br s, 1H, BMD), 5.06 (d, J=1 Hz, 1H, BMD), 5.03 (d, J=1 Hz, 1H, BMD), 5.01 (br s, 1H, BMD), 3.98 and 3.95 (AB quartet, $J_{21\text{-}21'}$=10 Hz, 1H each, H_{21} and $H_{21'}$), 2.81 (br d, $J_{12\alpha,12\beta}$=13 Hz, 1H, $H_{12\alpha}$), 2.59 (d, $J_{12\alpha,12\beta}$=13 Hz, 1H, $H_{12\beta}$), 2.52 (tdd, $J_{6ax\text{-}6eq}$=13 Hz, $J_{6ax\text{-}7eq}$=5 Hz, $J_{6ax\text{-}4}$=1 Hz, 1H, H_{6ax}), 2.47 (ddd, $J_{6ax\text{-}6eq}$=13 Hz, $J_{6eq\text{-}7ax}$=5 Hz, $J_{6eq\text{-}7eq}$=3 Hz, 1H, H_{6eq}), 2.30-2.05, 2.00-1.75 and 1.54-1.18 (overlapping m), 1.46 (s, 3H, C_{19} methyl), 0.86 (s, 3H, C_{18} methyl); ^{13}C NMR ($CDCl_3$) δ 209.94 (C_{11}), 181.60 (C_3), 170.07 (C_5), 146.34

(C_2), 124.09 (C_1), 121.77 (C_4), 109.42 (C_{20}), 94.96 (C_{22}), 91.78 (C_{23}), 90.45 (C_{17}), 69.86 (C_{21}), 61.16 (C_9), 50.47 (C_{12}), 50.24 (C_{14}), 49.63 (C_{13}), 42.73 (C_{10}), 35.65 (C_8), 33.64 (C_7), 32.25 (C_6), 31.98 (C_{16}), 23.30 (C_{15}), 19.76 (C_{19}), 13.70 (C_{18}); IR ($CDCl_3$) 3425 (br,m,O-H), 1705 and 1640 (s,CO), 1605 (w,C=C) cm^{-1} [Lit.[17] 3448, 1709, 1644, 1618]; MS (CI, methane, 70 ev), m/e 417 (MH^+, 100%); MS (EI, 55 ev), m/e 416 (M^+, 100%), 386 (M-CH_2O, 71%), 368 (M-CH_2O-H_2O, 7%), 356 (M-CH_2O-CH_2O, 24%), 338 (M-CH_2O-CH_2O-H_2O, 12%), 327 (M-CH_2O-CH_2O-HCO, 6%), 297 (M-$C_4H_7O_4$, 9%), 279 (M-$C_4H_7O_4$-H_2O, 4%); UV (CH_3OH) λ_{max} (ϵ_{max})= 250.8 (10220) nm [Lit.[17] 252 (11220).

18g: mp (acetone-hexane) 200-205 °C; R_f 0.69; ^1H NMR ($CDCl_3$) δ 6.35 (s, 1H, OH), 6.33 (s, 1H, H_1), 6.17 (d, $J_{4,6ax}$=1.0 Hz, 1H, H_4), 5.20 (br s, 1H, BMD), 5.04 (d, J=1 Hz, 1H, BMD), 5.03 (br s, 1H, BMD), 5.02 (d, J=1 Hz, 1H, BMD), 4.00 and 3.98 (AB quartet, $J_{21\text{-}21'}$=9 Hz, 1H each, H_{21} and $H_{21'}$), 2.49 (tdd, $J_{6ax\text{-}6eq}$=12.5 Hz, $J_{6ax\text{-}7eq}$=5 Hz, $J_{6ax\text{-}4}$=1.5 Hz, 1H, H_{6ax}), 2.42 (ddd, $J_{6ax\text{-}6eq}$=12.5 Hz, $J_{6eq\text{-}7ax}$=5 Hz, $J_{6eq\text{-}7eq}$=3 Hz, 1H, H_{6eq}), 2.02-1.56, 1.44-1.02 and 1.00-0.81 (overlapping m), 1.24 (s, 3H, C_{19} methyl), 0.88 (s, 3H, C_{18} methyl); ^{13}C NMR ($CDCl_3$) δ 181.53 (C_3), 172.86 (C_5), 146.02 (C_2), 124.39 (C_1), 120.96 (C_4), 109.82 (C_{20}), 94.85 (C_{22}), 91.52 (C_{23} and C_{17}), 70.14 (C_{21}), 53.16 (C_9), 50.72 (C_{14}), 46.56 (C_{13}), 44.10 (C_{10}), 35.07 (C_8), 33.80 (C_7), 32.84 (C_6), 31.62 (C_{16}), 30.49 (C_{12}), 23.87 (C_{15}), 22.56 (C_{11}), 19.71 (C_{19}), 12.71 (C_{18}); IR ($CDCl_3$) 3430 (br,m,O-H), 1645 (s,CO), 1600 (w,C=C) cm^{-1}; MS (CI, methane, 60 ev), m/e 403 (MH^+, 100%), 373 (MH^+-CH_2O, 31%), 355 (MH^+-CH_2O-H_2O, 41%), 343 (MH^+-CH_2O-CH_2O, 22%), 337 (MH^+-CH_2O-H_2O-H_2O, 3%), 325 (MH^+-CH_2O-CH_2O-H_2O, 22%), 315 (MH^+-$C_3H_4O_3$, 15%), 313 (MH^+-$C_3H_6O_3$, 9%), 285 (MH^+-$C_4H_6O_4$, 19), 267 (MH^+-$C_4H_6O_4$-H_2O, 2%); UV (CH_3OH) λ_{max} (ϵ_{max})= 253.6 (12600) nm; Anal. Calcd for $C_{23}H_{30}O_6$: C, 68.64; H, 7.51. Found:C, 68.91; H, 7.69.

General Photooxidation Procedure: The photooxidation apparatus previously described[14a] was charged with 5 mL of a $CHCl_3$ (for **15**) or CH_2Cl_2 (for **18**) containing equimolar amounts (generally 0.5 mmol) of enol and tetramethylammonium fluoride hexahydrate (Aldrich), as well as polymer-based Rose Bengal (Dye Tel Inc., POB 23, Perrysburg, Ohio) to serve as photosensitizer. [Caution: The ammonium fluoride salt is hygroscopic and the efficiency of the reaction decreases dramatically if this reagent or the solvent is wet.] During the course of the irradiation, the reaction vessel was constantly flushed with oxygen and the reaction mixture was vigorously magnetically stirred. Irradiation times (see Table 1) were determined by the progress of the reaction which was followed by TLC. The product mixture was then worked-up by filtering off the polymer-based Rose Bengal, evaporating the solvent, dissolving the residue in ether, washing the latter thrice with 10% HCl and drying over $MgSO_4$. The solvent was removed and the product was then purified by column chromatography on silica gel and/or recrystallization. The products were identified by their spectral data (^1H and ^{13}C NMR, IR, UV and MS) which in the case of **16a**[6e] and **19a-19d**[3] have already been reported in full. In the case of **15b**, **16b** was accompanied by the formation of **26**. The data for **16b**, **26** and **19e-19g** are reported below. In addition **19g** was independently synthesized via the previously described[3] base catalyzed autoxidation of **18** ("direct method").

16b: mp (acetone-hexane) 133.0-133.5 °C; R_f 0.13; ^1H NMR ($CDCl_3$) δ 7.38-7.21 (m, 11H, aromatic and H_3), 6.20 (d, $J_{2,3}$=10 Hz, 1H, H_2), 6.17 (brd, $J_{5\text{-}OH}$=6 Hz, 1H, H_5), 4.08 (brd, $J_{5\text{-}OH}$=6 Hz, 1H, OH),; ^{13}C NMR ($CDCl_3$) δ 128.8-127.7 (br signals perhaps due to epimerization, aromatic), 162.99 (C_1), 151.09 (C_3), 119.81 (C_2), 99.22 (C_5), 53.30 (C_4); MS (55 eV, CI-methane), *m/e* 267 (MH^+, 9.06%), 249 (MH^+-H_2O, 19.02%), 237 (MH^+-HCOH, 2.65%), 221 (MH^+-HCO_2H, 21.06%), 220 (Ph_2C=CH-HC=C=O, 27.39%); MS (55 eV, EI), *m/e* 267 (MH^+, 0.2%), 249 (MH^+-H_2O, 0.65%), 237 (M-HCO, 1.1%), 220 (Ph_2C=CH-HC=C=O, 100%), 203 (7.34%), 191 (Ph_2C=C=CH, 92.93%), 178 (Ph_2C_2, 6.9%), 165 ($PhCC_6H_4$, 22.31%), 114 (M-COOCHOH-PhH, 17.12%); FTIR (KBr) 3408.5 (br, m, O-H), 1703.4 (br, s, CO) cm^{-1}; UV ($CHCl_3$) λ_{max} (ϵ_{max})= 198.1 (3062), 240.6 (1478) and 270 (shoulder) nm; Anal. Calcd for $C_{17}H_{14}O_3$: C, 76.67; H, 5.30. Found:C, 76.53; H 5.37.



26

26: R_f (25% acetone in hexane) 0.23; ^1H NMR ($CDCl_3$) δ 7.40-6.99 (m, 20H, aromatic), 7.37 (dd, $J_{2,3}$=10 Hz, $J_{3,5}$=2 Hz, 1H, H_3), 7.20 (d, $J_{3,5}$=2 Hz, 1H, H_5), 6.16 (d, $J_{2,3}$=10 Hz, 1H, H_2), 5.81 (t, H_X of ABX system, J_{AX}=J_{BX}=7.5 Hz, $H_{3'}$), 2.96 and 2.84 (H_A and H_B of ABX system, J_{AB}=17 Hz, J_{AX}=J_{BX}=7.5 Hz, 1H each, $H_{2'}$); ^{13}C NMR ($CDCl_3$) δ 168.64 ($C_{1'}$), 160.32 (C_1), 150.24 (C_3), 145.38 ($C_{4'}$), 141.74 and 140.11 (ipso of $C_{4'}$ gem-diphenyl groups), 141.63 and 138.80 (ipso of C_4 gem-diphenyl groups), 130-127 (aromatic), 118.94 (C_2), 118.63 ($C_{3'}$), 95.03 (C_5), 51.58 (C_4), 34.97 (C_2) - assignments were based upon a comparison of these spectral data with those of lactol **15b** and of methyl 4,4-diphenylbut-3-enoate[12] and were confirmed by two-dimensional carbon-proton correlation experiments optimized for one-bond and long range interactions, respectively.; MS (55 eV), *m/e* 486 (M^+, 13.19%), 237 (Ph_2C=$CHCH_2CO_2$, 3.78%), 249 (M^+-Ph_2C=$CHCH_2CO_2$, 5.40%), 220 (Ph_2C=CH-HC=C=O, 100%), 207 (Ph_2C=HC-C=O, 10.52%), 193 (35.01%), 192 (24.12%), 191 (Ph_2C=C=CH, 39.94%), 177 (Ph_2C_2, 15.27%), 165 ($PhCC_6H_4$, 10.63%); FTIR (KBr pellet) 1738 (br, s, CO) cm^{-1}; UV (methanol) λ_{max} (ϵ_{max})= 205.9 (84909) and 245 (shoulder, 25225) nm.

19e (epimeric mixture α:β = 87:13): mp (acetone-hexane) 210-215 °C [Lit.[18] analytical sample: 220-223°]; R_f 0.48 (acetone-hexane 1:1); ^1H and ^{13}C NMR data for each epimer are given below and are based on the spectrum of the mixture; IR ($CDCl_3$) 3575 and 3300 (br,w,O-H), 1725 and 1700 (s,CO), 1630 (w,C=C) cm^{-1} [Lit.[18] 3571, 3300, 1727, 1700, 1633]; MS (CI, methane, 70 ev), m/e 333 (MH^+, 100%), 315 (MH^+-H_2O, 54%), 303 (MH^+-CH_2O, 5%), 297 (MH^+-H_2O-H_2O, 14%), 286 (MH^+-H_2O-HCO, 18%), 273 (MH^+-H_2O-$COCH_2$, 10%), 259 (MH^+-H_2O-OCOCHOH, 3%), 257 (MH^+-H_2O-HCO-HCO, 2%); MS (EI, 45 ev), m/e 333 (MH^+, 1%), 332 (M^+, 0.1%), 287 (M-OCHO, 21%), 286 (M-HOCHO, 100%); UV (CH_3OH) λ_{max} (ϵ_{max})= 226.0 (10900) nm [Lit.[18] 226.5 (14300).

19e-α epimer: ^{1}H NMR ($CDCl_3$) δ 5.72 (br d, $J_{4,6ax}$=2.0 Hz, 1H, H_4), 5.49 (br s, 1H, H_1), 4.72 (s, 1H, OH), 2.56 (br t, J=9 Hz, 1H, H_{17}), 2.48-2.32 (2H,m), 1.88-1.62 (5H,m) and 1.61-1.42 (5H, m), 2.12 (s, 3H, C_{21} methyl), 1.21 (s, 3H, C_{19} methyl), 0.66 (s, 3H, C_{18} methyl); ^{1}H NMR (d_6-acetone) δ 6.51 (br s, 1H, OH), 5.62 (dd, J=2.0 and 1.5 Hz, 1H, H_4), 5.42 (br s, 1H, H_1), 2.64 (br t, J=9 Hz, 1H, H_{17}), 2.49-2.42 (2H,m), 2.22-2.10 (m), 1.90-1.46 (m),1.32-1.00 (m), 1.22 (s, 3H, C_{19} methyl), 0.67 (s, 3H, C_{18} methyl); ^{13}C NMR ($CDCl_3$) δ 209.44 (C_{20}), 164.99 (C_5), 112.96 (C_4), 100.20 (C_1), 63.50 (C_{17}), 56.65 (C_{14}), 44.53 (C_9), 43.87 (C_{13}), 41.94 (C_{10}), 38.27 (C_{12}) 34.89 (C_8), 31.50 (C_{21}), 30.91 (C_6), 30.36 (C_7), 24.51 (C_{15}), 22.77 (C_{16}), 20.82 (C_{11}), 17.92 (C_{19}), 13.23 (C_{18}) [Resonance for C_3 not detected; may coincide with C_5].

19e-β epimer: ^{1}H NMR ($CDCl_3$) δ 5.38 (br s, 1H, H_1), 1.18 (s, 3H, C_{19} methyl); ^{1}H NMR (d_6-acetone) δ 6.57 (br s, 1H, OH), 5.64 (dd, J=2.0 and 1.5 Hz, 1H, H_4), 5.38 (br s, 1H, H_1), 1.18 (s, 3H, C_{19} methyl) - the remaining data is obscured by the α epimer; ^{13}C NMR ($CDCl_3$) δ 207.19 (C_{20}), 164.18 (C_5), 113.43 (C_4), 101.85 (C_1), 63.58 (C_{17}), 56.06 (C_{14}), 49.89 (C_9), 43.72 (C_{13}), 43.44 (C_{10}), 38.74 (C_{12}), 35.88 (C_8), 31.58 (C_{21}), 31.42 (C_6), 31.23 (C_7), 24.51 (C_{15}), 22.96 (C_{16}), 22.64 (C_{11}), 13.37 (C_{18}), 11.64 (C_{19}) [Resonance for C_3 not detected; may coincide with C_5].

19f: mp (acetone-hexane) 228-231 °C [Lit.[19] analytical sample: 230-233°]; R_f 0.39 (1:1 acetone-hexane); ^{1}H NMR ($CDCl_3$) δ 6.18 (br s, 1H, H_1), 5.74 (br s, 1H, H_4), 5.20, 5.06, 5.03 and 5.01 (each br s, each 1H, BMD), 3.98 (br s, 2H each, H_{21}), 2.87 (br d, $J_{12\alpha,12\beta}$=14 Hz, 1H, $H_{12\alpha}$), 2.59 (d, $J_{12\alpha,12\beta}$=14 Hz, 1H, $H_{12\beta}$), 2.69-2.52, 2.52-2.12, 2.10-1.70 and 1.60-1.10 (overlapping m), 1.26 (s, 3H, C_{19} methyl), 0.82 (s, 3H, C_{18} methyl); ^{13}C NMR ($CDCl_3$) δ 211.30 (C_{11}), 163.82 (C_3), 162.62 (C_5), 113.76 (C_4), 109.41 (C_{20}), 99.47 (C_1), 94.93 (C_{22}), 91.79 (C_{23}), 90.74 (C_{17}), 69.79 (C_{21}), 55.67 (C_9), 49.96 (C_{12}), 49.70 (C_{14}), 48.97 (C_{13}), 41.60 (C_{10}), 35.41 (C_8), 31.82 (C_{16}), 30.91 (C_6), 30.59 (C_7), 23.37 (C_{15}), 17.39 (C_{19}), 13.88 (C_{18}); IR ($CDCl_3$) 3350 (br,m,O-H), 1725 and 1700 (s,CO), 1605 (w,C=C) cm^{-1} [Lit.[19] 3448-3333, 1727, 1703, 1639-1612]; MS (CI, methane, 60 ev) m/e 421 (MH^+, 100%), 403 (MH^+-H_2O, 64%), 391 (MH^+-CH_2O, 6%), 373 (MH^+-H_2O-CH_2O, 19%), 355 (MH^+-$2H_2O$-CH_2O, 2%), 279 (MH^+-H_2O-$C_4H_6O_4$, 2%); UV (CH_3OH) λ_{max} (ϵ_{max})= 224.1 (13900) nm [Lit.[19] 224 (14500)].

19g: mp (acetone-hexane) 222-227 (dec.) °C; R_f 0.14; ^{1}H NMR ($CDCl_3$) δ 5.72 (d, J_{6ax}=2 Hz, 1H, H_4), 5.45 (s, 1H, H_1), 5.20, 5.06, 5.055 and 5.04 (each br s, each 1H, BMD), 4.00 and 3.98 (AB quartet, $J_{21,21'}$=8 Hz, 1H each, H_{21} and $H_{21'}$), 2.50-2.31, 1.91-1.63 and 1.59-0.75 (overlapping m), 1.24 (s, 3H, C_{19} methyl), 0.86 (s, 3H, C_{18} methyl); ^{13}C NMR ($CDCl_3$) δ 164.55 (C_3), 163.36 (C_5), 113.07 (C_4), 109.91 (C_{20}), 94.91 (C_{22}), 91.80 (C_{17}), 91.58 (C_{23}), 70.21 (C_{21}), 44.35 (C_9), 50.89 (C_{14}), 46.25 (C_{13}), 41.95 (C_{10}), 34.73 (C_8), 31.56 (C_{16}), 30.90 (C_6), 30.31 and 30.28 (C_7 and C_{12}), 23.88 (C_{15}), 20.22 (C_{11}), 18.01 (C_{19}), 12.58 (C_{18}); IR ($CDCl_3$) 3360 (br,m,O-H), 1740, 1695 (s,CO), 1650 (w,C=C) cm^{-1}; MS (CI, methane, 60 ev), m/e 407 (MH^+, 100%), 389 (MH^+-H_2O, 0.7%), 377 (MH^+-CH_2O, 1.5%), 361 (MH^+-H_2O-CO, 1.3%), 359 (MH^+-CH_2O-H_2O, 5%), 347 (MH^+-CH_2O-CH_2O, 0.17%); UV (CH_3OH) λ_{max} = 226.3 nm; Anal. Calcd for $C_{22}H_{30}O_7$: C, 65.01; H, 7.44. Found:C, 65.10; H 7.72.

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4. An extensive review of the oxygenation (including free radical autoxidation, BCA, singlet oxygenation and $O_2^{-\bullet}$ mediated oxidations) of enones and related enols and enolates has recently appeared; see Frimer, A.A. In "The Chemistry of Enones - Part 2"; Patai, S. and Rappoport, Z., Eds.; Wiley, New York, 1989; pp. 781-921.

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8. The preparation of the enols of cortisone and cortexolone (**18f** and **18g** respectively, where R'=OH and R"=$COCH_2OH$) could not be effected unless the dihydroxyacetone side chain was converted to the corresponding bismethylenedioxy (BMD) derivative.[7] Exploratory studies on the low temperature t-butoxide mediated BCA of cortisone and cortisone acetate indicated the formation of adrenosterone and other D-ring oxidation products. The base catalyzed oxidative degradation of members of the cortisone family to the corresponding 17-ketosteroid is well precedented.[9]

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