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Photochemistry of Estr-4-en-3-ones: 17β-Hydroxy-4-estren-3-one, 17β-Acetoxy-4,9-estradien-3-one, 17β-Hydroxy-4,9,11-estratrien-3-one, and Norgestrel. Photochemistry of 5α-Estran-3-ones[1a]

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The photochemistry of estr-4-en-3-ones **1a,b** is solvent dependent, yielding estr-5-en-3-ones **2** in ethyl acetate or 5α-estran-3-ones **3** in alcoholic solvents. Further irradiation of 5α-estran-3-ones **3** in alcoholic solvent yields the 2,3- and 3,4-seco-5α-estrane 3-esters **4** and **5** and the 2,3-secoestr-1-en-3-al (**6**). Photolysis of estra-4,9-dien-3-one **7** yields the photodimer **8** whereas the estra-4,9,11-trien-3-one **9** yielded polymer.

The photochemistry of 3-keto 4-ene and 3-keto 4,6-diene substituted androstenes has been extensively investigated. A wide variety of photochemical reactions have been reported for this system including photoisomerization to yield lumiproducts or β,γ-unsaturated ketones, solvent addition, cycloaddition, reduction, and dimerization.[2] The type of reaction that occurs is largely dependent upon the extent of conjugation and the solvent used.

By comparison, the 3-keto-4-estrenes (3-keto-19-norandrost-4-enes) **1a** and **1b** have received very little attention. Irradiation of 17β-hydroxy-4-estren-3-one (**1a**) in *tert*-butyl alcohol and dioxane was reported to lead to dimerization and hydrogen atom abstraction but no products were isolated.[3] 3-Keto-4-estrenes and 3-keto-4,9-estradienes have been used as photoaffinity labels.[4,5] Photolysis of 9α,10α- and 9β,10β-oxidoestr-4-en-3-ones resulted in the epoxide ring being isomerized to two novel steroid skeletons.[6] Furthermore, since many 3-keto-4-estrenes are in clinical use, it seemed advisable to photolyze these molecules in order to obtain the photoproducts that may potentially be formed in patients taking these preparations[7] and to determine the biological properties of these photoproducts.

Of the four steroids selected for this study, three, 17β-hydroxyestr-4-en-3-one (**1a**), 17β-hydroxyestra-4,9-dien-3-one (**7**), and 17β-hydroxyestra-4,9,11-trien-3-one (**9**) have the same estrane skeleton but differ in the extent of conjugated unsaturation with the carbonyl. The fourth, 13β-ethyl-17α-ethynyl-17β-hydroxygon-4-en-3-one (**1b**) is the oral contraceptive norgestrel.[8] It is a 3-keto-4-estrene with an ethyl group replacing the methyl group at C-13 and 17α-ethynyl-17β-hydroxyl groups.

Results and Discussion

Photolysis of the 3-keto-4-estrenes **1a** and **1b** with a 450-w Hanovia lamp through a Pyrex filter gave the β,γ-unsaturated ketones **2a** and **2b** when carried out in the neutral solvent ethyl acetate. The NMR spectrum of the 3-keto-5-estrenes **2a** and **2b** showed characteristic multiplets at δ 5.50 and 5.45, respectively, due to the C-6 olefinic hydrogen. Photolysis of the 17β-acetoxyandrost-4-en-3-one (**1c**) in the neutral solvent benzene also afforded the photoisomerization product 17β-acetoxyandrost-5-en-3-one (**2c**), together with a cyclobutane photodimer.[9]

Irradiation of the estrenones **1a** and **1b** in the polar solvent methanol gave the saturated estran-3-ones **3a** and **3b** in 20% and 10% yields, respectively. A similar photoreduction reaction was observed when the androst-4-en-3-one (**1c**) was irradiated in isopropyl alcohol to yield

(1) (a) For the previous paper in this series, see: Williams, J. R.; Abdel-Magid, A.; Ricker, W.; Salama, H. *J. Org. Chem.* **1982**, *47*, 2536. (b) Temple University. (c) Hoffmann-LaRoche, Inc.

(2) For reviews of enone photochemistry, see: (a) Schuster, D. I. In "Rearrangements in Ground and Excited States"; De Mayo, P., Ed.; Academic Press: New York, 1980; Vol. 3, pp 167–279. (b) Schaffner, K. *Tetrahedron* **1974**, *30*, 1891. (c) Fried, J., Edwards, J. A., Ed. "Organic Reactions in Steroid Chemistry"; Van Nostrand Reinhold Co.: New York, 1972; Vol. II, p 288.

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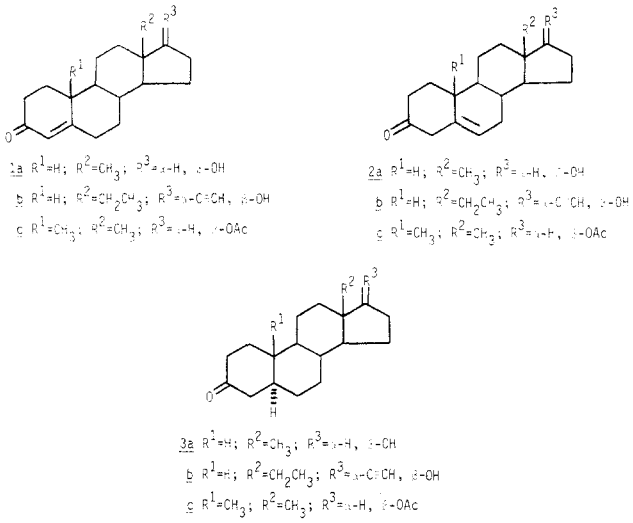


1a R^1=H; R^2=CH_3; R^3=α-H, β-OH
b R^1=H; R^2=CH_2CH_3; R^3=α-C≡CH, β-OH
c R^1=CH_3; R^2=CH_3; R^3=α-H, β-OAc

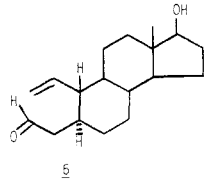
2a R^1=H; R^2=CH_3; R^3=α-H, β-OH
b R^1=H; R^2=CH_2CH_3; R^3=α-C≡CH, β-OH
c R^1=CH_3; R^2=CH_3; R^3=α-H, β-OAc

3a R^1=H; R^2=CH_3; R^3=α-H, β-OH
b R^1=H; R^2=CH_2CH_3; R^3=α-C≡CH, β-OH
c R^1=CH_3; R^2=CH_3; R^3=α-H, β-OAc

the saturated androstan-3-one **3c**.[10] In the case of **1b** a mixture of A-seco methyl esters **4b** and **5b** was also isolated in 2.5% yield. The proton NMR spectrum showed two methyl ester singlets at δ 3.21 and 3.13 and the infrared showed two acetylenic stretching vibrations at 2106 and 2245 cm^{-1}. The photolysis of **1a** and **1b** using a Pyrex filter proceeded much slower in *tert*-butyl alcohol than in methanol, so a quartz filter was used. Photolysis of **1a** afforded the saturated ketone **3a** in 12% yield together with a mixture of *tert*-butyl esters **4a** and **5a**. The ester

4a R^1=t-Bu; R^2=CH_3; R^3=α-H, β-OH
b R^1=CH_3; R^2=CH_2CH_3; R^3=α-C≡CH, β-OH

5a R^1=t-Bu; R^2=CH_3; R^3=α-H, β-OH
b R^1=CH_3; R^2=CH_2CH_3; R^3=α-C≡CH, β-OH

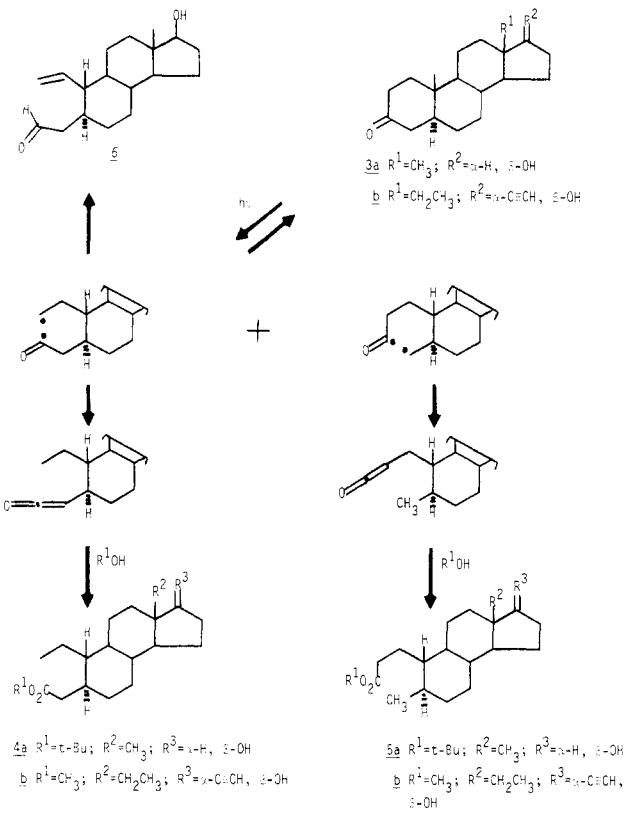


6

mixture showed infrared carbonyl absorption at 1708 and 1733 cm^{-1}. The ^{13}C NMR spectrum showed two ester carbonyls at 173.8 and 173.2 ppm. An unsaturated aldehyde (**6**) was also isolated in 1.0% yield. The aldehyde hydrogen gave rise to a multiplet at δ 9.78–9.70. Three olefinic hydrogens gave rise to a multiplet at 5.64–4.81 indicative of a vinyl substituent. The ^{13}C NMR spectrum showed an aldehyde carbonyl carbon at δ 202.3 and olefin C atoms at 141.4 (d) and 116.5 (t). Photolysis of **1b** in *tert*-butyl alcohol using a quartz filter afforded the saturated steroid, **3b**, in 6% yield, but no esters or aldehydes were isolated. The structures of the esters **4** and **5** and the aldehyde **6** are consistent with their spectral data and method of synthesis.

The formation of the esters **4** and **5** and of the aldehyde **6** can readily be explained as secondary photoproducts resulting from further irradiation of the primary photo-

Scheme I



6

3a R^1=CH_3; R^2=α-H, β-OH
b R^1=CH_2CH_3; R^2=α-C≡CH, β-OH

4a R^1=t-Bu; R^2=CH_3; R^3=α-H, β-OH
b R^1=CH_3; R^2=CH_2CH_3; R^3=α-C≡CH, β-OH

5a R^1=t-Bu; R^2=CH_3; R^3=α-H, β-OH
b R^1=CH_3; R^2=CH_2CH_3; R^3=α-C≡CH, β-OH

product, the photoreduction product **3**. Cyclohexanones undergo facile photolysis to acyl–alkyl radical pairs followed by intramolecular hydrogen atom abstraction to yield a ketene and/or an unsaturated aldehyde.[11] Since the C-3 ketone is not symmetrical, two different α-cleavage reactions occur, giving rise to two different esters as outlined in Scheme I. This was confirmed by isolation of the same photoproducts from irradiation of **3a**. To our knowledge this is the first report of the photochemistry of saturated unsubstituted 3-keto steroids.

The photochemistry of androst-4-en-3-ones is strongly dependent upon the solvent used.[2a,10] As has been shown in this study the photochemistry of estr-4-en-3-ones is similarly very solvent dependent. However, photolysis of estr-4-en-3-ones in alcoholic solvents affords only photoreduction and no lumiproducts which were observed in the case of androst-4-en-3-ones. This difference may be explained by the absence of the C-19 methyl group which can facilitate the C-1,C-10 bond cleavage reaction which is on the pathway leading to the lumiproduct.[2a] Quenching and sensitization experiments have established that androst-4-en-3-ones undergo photorearrangement to lumiproducts and C=C bond reduction via a triplet π,π^* state,[2a] while reactions involving photoisomerization to the β,γ-unsaturated ketones, 5-en-3-ones, have been ascribed to triplet states with n,π^* character.[10]

Photolysis of the estra-4,9-dien-3-one **7** in methanol gave the crystalline photodimer **8** in 55% yield. The photodimer **8** easily thermalizes back to the starting dienone even at room temperature. The observed melting point of the dimer was essentially that of the monomer. Proton NMR showed the loss of the olefinic resonance, suggesting that photocycloaddition had occurred at the C-4,C-5 bond. This was supported by the infrared spectrum of the dimer

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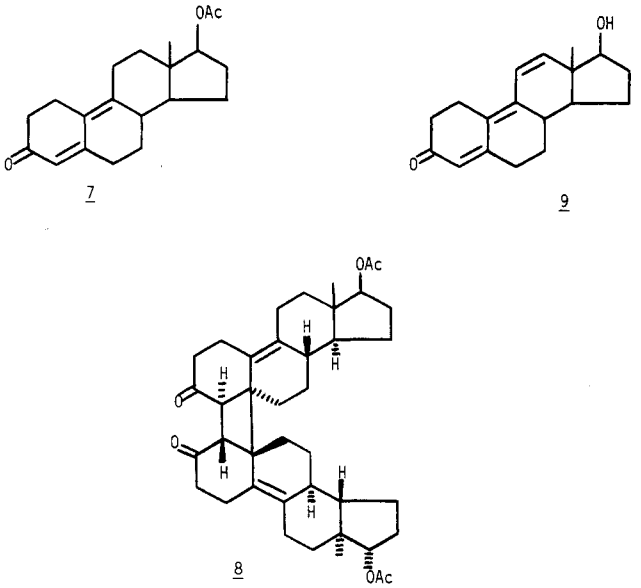
(11) For a review of saturated cyclic ketone photochemistry, see: Wagner, P. J. In "Rearrangements in Ground and Excited States"; De Mayo, P., Ed.; Academic Press: New York, 1980; Vol. 3, pp 381–444.



which showed carbonyl absorption at 1714 cm^{-1} vs. 1660 cm^{-1} for the dienone **4**. ^{13}C NMR revealed that there were two new sp^3 carbon resonances; one a singlet and the other a doublet, further supporting the idea of a symmetrical dimer. Treatment of the dimer with aluminum oxide, acid, or base resulted in no change in the photodimer, indicating that the new bonds generated in the photodimerization were the more thermodynamically stable cis configuration.[12] These observations were confirmed by a single-crystal X-ray analysis which established its structure as the head to head, anti photodimer (**8**) (Figure 1). The product is formed by the β-face of the C-4,C-5 double bond of one steroid, adding across the α-face of the C-4,C-5 double bond of the second molecule. The absence of the C-10 methyl group in the estra-4,9-dien-3-one **7** facilitating intermolecular interactions is probably the reason for its ready photodimer formation. This result is in agreement with the results of Rubin et al.,[13] who concluded that steric factors govern the mode of photocycloaddition of the C-4,C-5 olefin in androsta-4,6-dien-3-ones.

The ultraviolet spectrum of **9** showed λ_{max} 238 nm (ϵ 6450) and 341 nm (ϵ 30 300) characteristic of a linear conjugated trienone chromophore. However, irradiation of **9** in a variety of solvents including methanol, ethyl acetate, ether, acetone, dioxane, benzene, and 2-propanol consistently led to an uncharacterizable solid, probably polymer. The only noticeable solvent effect was in the amount of time it took to deplete the starting material, ranging from minutes in the case of ether to several hours in the case of 2-propanol. The precipitated solid had a melting point above 300 °C and could not be dissolved to any appreciable extent in almost all solvents. Photolysis of **9** in the solid state or in solution using benzophenone as a sensitizer gave no new materials. Likewise, irradiation of **9** in ether with tri-*n*-butylstannane to try to reduce any radicals formed led to polymeric solid. Attempts to photoadd ethylene, isobutylene, vinyl acetate, and cyclopentene failed to give adducts before the steroid was consumed. Thus, even though **9** absorbs light at long wavelengths, it should not act as a photoaffinity label.

Experimental Section

Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. IR spectra were taken in KBr with a Perkin-Elmer 225 spectrophotometer and FT-IR spectra were recorded on a Nicolet 6000 Fourier Transform infrared spectrometer. UV absorption spectra were measured in methanol on a Cary 14 spectrophotometer. NMR spectra were recorded at 100 MHz on a Varian XL-100 spectrometer fitted with a Nicolet NTCFT 1180 pulse system and at 90 MHz on a Perkin-Elmer R32 spectrometer. Chemical shifts are reported in δ (ppm) from the internal standard Me_4Si in chloroform-*d*. Low-resolution mass spectra were recorded on a Hitachi Perkin-Elmer RMU-6 H spectrometer, and high-resolution mass spectra were obtained on a Varian MAT CH5 spectrometer. A pyrex filter was used for photolysis except where noted. A molecular weight determination on **8** using osmometry was done by Galbraith Laboratories, Knoxville, TN. Norgestrel (Wyeth Co.) had the following: mp 204–206 °C (lit.[8] mp 203–206 °C). 17β-Hydroxy-4,9,11-estratrien-3-one had the following: mp 179–183 °C (lit.[14] mp 180–184 °C).

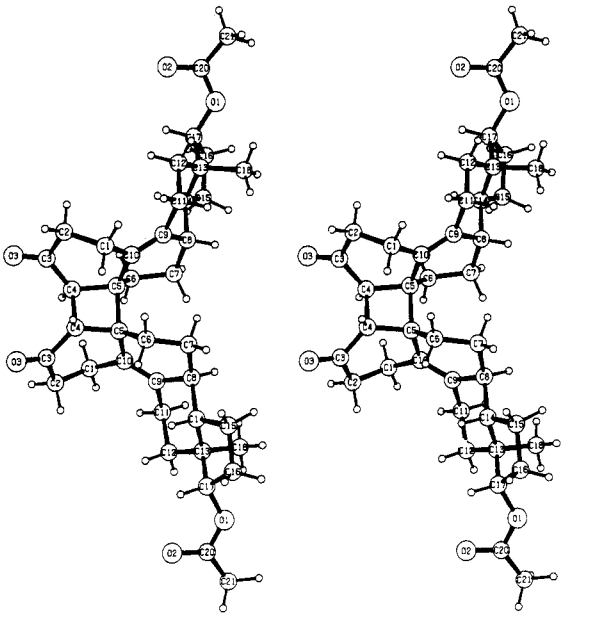


Figure 1. Stereoscopic drawing of the estra-4,9-dien-3-one photoproduct (**8**).

Photolysis of 17β-Hydroxyestr-4-en-3-one (1a) in Ethyl Acetate. A solution of the enone (**1a**) (1.0 g) in 450 mL of ethyl acetate, stirred with a stream of N_2 was irradiated with a 450-W Hanovia lamp through a Pyrex filter for 4 h. Solvent was removed in vacuo and the remaining gum chromatographed on silica gel (35 g). Elution with 150 mL of hexane–ether (1:1) gave 215 mg (21%) of 17β-hydroxyestr-5-en-3-one (**2a**), identical with an authentic sample.[15] The identity was establish by comparison of IR and NMR spectra and by melting point and mixture melting point, 105–106 °C. The remainder of the reaction was starting enone and more polar materials which could not be separated.

Photolysis of 13β-Ethyl-17α-ethynyl-17β-hydroxygon-4-en-3-one (Norgestrel) (1b) in Ethyl Acetate. Photolysis of **1b** (1 g) in ethyl acetate (500 mL) for 5 h and workup as described above gave upon chromatography on silica gel (45 g) and elution with ether–benzene (1:4) the unconjugated enone **2b** (0.4 g, 40%): mp 127–129 °C: FT-IR (KBr) 3378 (OH), 3268 (alkyne CH), 2098 (C≡C), 1705 (C=O), 1673, 1659 (C=C), 1458, 1449, 1435, 1427, 1403, 1343, 1324, 1293, 1256, 1186, 1128, 1065, 1043, 1029, 690, 655, 644 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.45 (m, 1 H), 2.99 (br s, 2 H), 2.75 (br s, 1 H), 2.59 (s, 1 H), 1.04 (t, 3 H); ^{13}C NMR δ 209.1 (s), 135.1 (s), 122.4 (d), 81.3 (s), 73.8 (t), 51.2 (d), 50.2 (t), 48.1 (s), 44.6 (d), 42.5 (d), 40.5 (d), 39.5 (d), 36.9 (d), 30.6 (t), 30.4 (t), 28.4 (t), 27.0 (t), 22.4 (t), 18.8 (t), 18.7 (s), 9.4 (q); mass spectrum, *m/z* (relative intensity) 313 (M + H, 100), 296 (9), 295 (M + H – H_2O, 33), 293 (4), 245 (3), 189 (4), 173 (3), 159 (6), 149 (5), 135 (5), 133 (10), 123 (7). Anal. Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.35, H, 9.07.

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(13) Rubin, M. B.; Hipps, G. E.; Glover, D. *J. Org. Chem.* **1964**, *29*, 68.
(14) Heller, M.; Lenhard, R. H.; Bernstein, S. *Steroids* **1967**, *10*, 211.
(15) Rizvi, S. Q. A.; Williams, J. R. *J. Org. Chem.* **1980**, *46*, 1127.

Photolysis of 17β-Hydroxyestr-4-en-3-one (1a) in *tert*-Butyl Alcohol. Irradiation of **1a** (4.5 g) in *tert*-butyl alcohol (1300 mL) for 9 h using a quartz filter afforded a residue following the normal workup. Flash column chromatography on silica gel (200 g) using 15% ethyl acetate in hexane as an initial eluent gave two products (0.22 g, 5%). This fraction was further chromatographed by using 10% ether in hexane to give an inseparable mixture of the two isomeric *tert*-butyl esters **4a** and **5a** (0.149 g) as a colorless oil: FT-IR (neat) 3440, 3429, 3406, 3396, 2952, 2922, 2868, 1733, 1708 (two ester carbonyls), 1454, 1421, 1392, 1367, 1335, 1310, 1297, 1257, 1216, 1151, 1113, 1071, 1054, 1028, 954, 848, 762, 666 cm^{-1}; ^1H NMR δ 3.64 (t, J = 8 Hz, 1 H), 2.57–0.75 (m, 25 H), 1.48 (s, 9 H), 0.74 (s, 3 H), ^{13}C NMR δ 173.8, 173.2 (s, two ester CO), 82.0 (d, C-17), 28.1 (q, *t*-Bu Me's), 11.1 (q, C-18); mass spectrum, m/z (relative intensity) 350 (85), 349 (10), 348 (36), 337 (5), 336 (5), 332 (14), 320 (4), 294 (14), 277 (17), 249 (16), 117 (6), 58 (100); high-resolution mass spectrum, calcd for $C_{22}H_{38}O_3$ 350.2821, found 350.2852. The second product (55 mg) was the aldehyde **6**; ^1H NMR δ 9.78–9.70 (m, 1 H), 5.64–4.81 (m, 3 H), 3.67 (t, J = 3.7 Hz, 1 H), 2.62–0.81 (m, 20 H), 0.78 (s, 3 H); ^{13}C NMR δ 202.3 (d), 141.4 (d), 116.5 (t), 81.6 (d), 53.8 (d), 50.2 (t), 49.2 (d), 47.1 (d), 43.1 (s), 11.01 (q), and others; high-resolution mass spectrum, calcd for $C_{18}H_{28}O_2$ 276.2089, found 276.2075. Further elution provided the saturated ketone **3a** as a solid (0.54 g, 12%): mp 127–128 °C (ether–hexane) (lit.[16] mp 130–131 °C); FT-IR (KBr) 3313 (OH), 1717 (C=O), 1453, 1443, 1430, 1419, 1385, 1356, 1329, 1319, 1267, 1248, 1219, 1202, 1175, 1143, 1128, 1095, 1074, 1057, 1026, 1015, 955, 529 cm^{-1}; ^1H NMR δ 3.68 (t, J = 8 Hz, 1 H), 2.57–0.89 (m, 24 H), 0.84 (s, 3 H); mass spectrum, m/z (relative intensity) 277 (M + H, 100), 276 (8), 275 (14), 260 (5), 259 (28), 258 (3), 257 (9), 241 (11). Further elution provided the unreacted enone **1a** (1.2 g, 27%) and finally a very polar mixture (1 g, 22%); its components were not identified.

Photolysis of 3a in *tert*-Butyl Alcohol. Photolysis of **3a**[16] (1.5 g) in *t*-butyl alcohol (120 mL) for 7 h using a quartz filter afforded a gum upon evaporation of the solvent. Flash column chromatography of the gum on silica gel as described above gave the same inseparable mixture of **4a** and **5a** (100 mg), and a trace of the aldehyde **6** as proven by TLC and ^1H NMR.

Photolysis of 1a in Methanol. A solution of **1a** (1.2 g) in methanol (1.2 L) was photolyzed for 9 h and worked up as described above. The resulting gum (1.22 g) was chromatographed on silica gel (40 g). Initial elution with 200 mL of hexane–ethyl acetate (3:1) afforded 249 mg (20%) of 17β-hydroxyestran-3-one (**2a**) which was recrystallized from hexane–ether, mp 126–128 °C (lit.[16] mp 130–131 °C). Continued elution with the same solvent gave 220 mg (18%) of **1a** and uncharacterizable mixtures.

Photolysis of 13β-Ethyl-17α-ethynyl-17β-hydroxygon-4-en-3-one (1b) in Methanol. Irradiation of **1b** (5 g) in methanol (1400 mL) for 9 h and workup as described above gave a gum. Flash column chromatography on silica gel (300 g) using 15% ethyl acetate in hexane afforded a fraction (0.8 g, 16%) that contained two major components as determined by TLC. Rechromatography of this fraction with 10% ether in hexane provided a minor product (0.12 g, 2.5%), an inseparable mixture of the two methyl esters **4b** and **5b** as a colorless oil which solidified to a glassy mass: FT-IR (KBr) 3423, 3407 (OH), 2936, 2873 (CH), 2245, 2106 (C≡C), 1701 (C=O), 1458, 1447, 1395, 1386, 1375, 1362, 1336, 1297, 1287, 1271, 1250, 1226, 1217, 1210, 1197, 1174, 1143, 1128, 1102, 1065, 1044, 1034, 983, 967, 922, 889, 866, 733, 645, 621, 615, 515 cm^{-1}; ^1H NMR δ 3.21 (s, OMe), 3.13 (s, OMe), 2.55 (s, ≡CH, 1 H), 2.45–1.0 (m, 27 H), 0.95 (t, 3 H); mass spectrum, m/z (relative intensity) 347 (M + H, 4), 344 (8), 343 (31), 330 (18), 329 (77), 316 (23), 315 (100), 313 (11), 311 (50), 309 (11), 298 (11), 297 (36), 205 (7), 191 (8), 179 (7), 177 (10), 139 (11), 133 (72); high-resolution mass spectrum, calcd for $C_{22}H_{34}O_3$ 346.25078, found 346.2501.

The second product (0.5 g, 10%) was the saturated ketone **3b**: mp 199–200 °C; FT-IR (KBr) 3371 (OH), 3269 (≡CH), 2097 (C≡C), 1699 (C=O), 1468, 1459, 1446, 1433, 1422, 1390, 1358, 1346, 1328, 1320, 1298, 1284, 1273, 1254, 1242, 1233, 1211, 1178, 1141, 1130, 1093, 1065, 1044, 1032, 932, 691, 654, 643, 608, 513 cm^{-1}; ^1H NMR δ 2.58 (s, 1 H), 2.52–1.04 (m, 24 H), 0.93 (t, 3 H); ^{13}C NMR δ 211.9 (s), 88.0 (s), 73.9 (d), 48.6 (s), 48.0 (s), 47.1 (d), 45.6 (d), 43.6 (d), 41.4 (d), 41.2 (t), 39.5 (t), 33.9 (t), 30.4 (t), 30.1 (t), 28.5 (t), 25.8 (t), 22.4 (t), 18.8 (t), 9.5 (q); mass spectrum, m/z (relative intensity) 315 (M + H, 100), 314 (5), 313 (8), 298 (7), 297 (28), 295 (6), 221 (10), 161 (16), 123 (6), 114 (34); high-resolution mass spectrum, calcd for $C_{21}H_{30}O_2$ 314.2245, found 314.2233. Further elution gave the unreacted enone **1b** (1.6 g, 32%) followed by a fraction containing at least three components (1.5 g, 30%); none of them was separated or identified.

Photolysis of 1b in *tert*-Butyl Alcohol. Irradiation of **1b** (5.0 g) in *tert*-butyl alcohol (1400 mL) for 10 h followed by the usual work up gave upon chromatography the saturated steroid **3b** (0.3 g, 6%), unreacted enone **1b** (1.26 g, 25%), and a mixture of unidentified products.

17β-Acetoxyestra-4,9-dien-3-one (7). 17β-Hydroxy-5(10)-estren-3-one was brominated and dehydrobrominated with pyridinium bromide perbromide to yield 17β-hydroxyestra-4,9-dien-3-one in 74% yield, mp 175–176 °C (lit.[17] mp 176 °C). Acetylation of the 17β-hydroxyl group with acetic anhydride/pyridine afforded 17β-acetoxyestra-4,9-dien-3-one (**7**) as prisms from ether–hexane: mp 106–107 °C; UV (CH_3OH) 303 nm (ε 20 500); IR (KBr) 1724 (acetate), 1660 (carbonyl), and 1607 cm^{-1} (olefinic); ^1H NMR δ 5.68 (s, 1, H-4), 4.64 (t, 1, H-17), 2.30 (s, 3, H-20 acetate), 0.96 (s, 3, H-18). Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.37; H, 8.23. Found: C, 76.16; H, 8.27.

Photolysis of 17β-Acetoxyestra-4,9-dien-3-one (7). A solution of **7** (450 mg) in 450 mL of methanol (degassed) was irradiated as described above. After 40 min, the solvent was carefully removed in vacuo (temperature less then 35 °C) so as to leave about 50 mL which when cooled yielded 250 mg (55%) of crystalline photodimer **8**: mp 108–109 °C; UV (CH_3OH) end absorption; IR (KBr) 1737 (acetate), 1714 (carbonyl), and 1667 cm^{-1} (olefin); ^1H NMR δ 4.60 (t, 2, H-17), 2.92 (s, 2, H-4 cyclobutane protons), 2.00 (s, 6, H-20 acetate), 0.98 (s, 6, H-18). Anal. Calcd for $C_{40}H_{52}O_6$: C, 76.39; H, 8.23. Found: C, 76.56; H, 8.27. Chromatography of the filtrate on silica gel and elution with hexane–ether (4:1) first gave **7** (20%) and then a 5% yield of a second dimer: mp 122–123 °C (hexane–ether); UV (CH_3OH) end absorption; IR (KBr) 1737 (acetate) and 1713 (carbonyl) cm^{-1}; ^1H NMR δ 4.65 (t, 2, H-17), 2.92 (s, 2, cyclobutane protons), 2.05 (s, 6, H-20 acetate), 0.95 (s, 6, H-18); molecular weight osmometry ($CHCl_3$) = 612; calcd for $C_{40}H_{52}O_6$, 628. Anal. Calcd for $C_{40}H_{52}O_6$: C, 76.39; H, 8.23. Found: C, 76.62; H, 8.27.

The dienone **7** was dissolved in ether and coated as a crystalline layer on the inside wall of a quartz test tube. The tube was filled with N_2 and photolyzed in a Rayonet reactor equipped with 300-nm wavelength Hg vapor lamps for 25 h. No dimer was formed and TLC showed only starting material.

X-ray Crystallography of Photodimer 8. The crystals of **8** were orthorhombic, space group 2_122_1, with a = 7.164 (1) Å, b = 9.555 (1) Å, c = 27.142 (4) Å, and d_{calcd} = 1.152 g/cm³ for Z = 2 ($C_{40}H_{52}O_6 \cdot CH_3OH$, M_r = 644.89). The intensity data were measured on a Hilger-Watts diffractometer Ni filtered CuKα radiation, θ-2θ scans, pulse height discrimination). A crystal measuring approximately 0.10 × 0.3 × 0.5 mm was used for data collection. A total of 1471 reflections were measured for θ < 57°, of which 1338 were considered to be observed [$I > 2.5\sigma(I)$]. The structure was solved by a multiple solution procedure[8] and was refined by full matrix least squares. In the final refinement isotropic temperature factors were used for the hydrogen atoms and the oxygen and carbon atoms of the methanol molecule, and anisotropic thermal parameters were used for the oxygen and carbon atoms of the dimer. The hydrogen atoms were included in the structure factor calculations but their parameters were not refined. The final discrepancy indices are R = 0.067 and ωR = 0.085 for the 1338 observed reflections. There is one peak (0.5 e A^{-3}) on the final difference map which is greater than ±0.2 e A^{-3}; this peak is found in the neighborhood of the acetate side chain.

Isomerizations of Photodimer 8. The photodimer **8** (50 mg) was dissolved in 30 mL of CH_2Cl_2 at 0 °C. To this solution was added basic aluminum oxide (1 g; activity I). After several days of stirring at room temperature there was no change in the dimer relative to a blank sample. Similar treatment of **8** in acetone with

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K-10 Montmorillonite Clay catalyst powder failed to isomerize 8.

Photolysis of 17β-Hydroxyestra-4,9,11-trien-3-one (9). Trienone **9** (10 mg) in 10 mL of solvent, was irradiated as described above. The reaction was monitored by TLC until **9** had all reacted. A variety of solvents including methanol, ethyl acetate, ether, acetone, dioxane, benzene, and isopropyl alcohol led to the formation of a polymeric solid, mp >300 °C, which precipitated out of solution.

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Supplementary Material Available: Table of anisotropic thermal parameters of **8** (8 pages). Ordering information is given on any current masthead page.

Registry No. **1a**, 434-22-0; **1b**, 797-63-7; **2a**, 42028-18-2; **2b**, 100021-05-4; **3a**, 1434-85-1; **3b**, 78088-19-4; **4a**, 100021-06-5; **4b**, 100021-07-6; **5a**, 100044-89-1; **5b**, 100021-08-7; **6**, 100021-09-8; **7**, 53303-85-8; **8**, 100021-10-1; **9**, 10161-33-8; 17β-hydroxy-5(10)-estren-3-one, 1089-78-7; 17β-hydroxyestra-4,9-dien-3-one, 6218-29-7.

A Stereoselective Total Synthesis of (±)-Muzigadial

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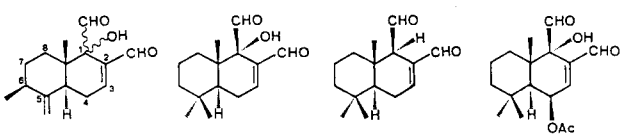
A stereoselective, 14-step, total synthesis of (±)-muzigadial (**1a**, 11% overall yield), starting from the commercially available Wieland–Miescher ketone (**5**), via intermediate ketone **13**, is described. The two additional chiral centers in **13** were incorporated by equilibration of the mixture of stereoisomeric ketones **10** to the most favorable isomer, **10a**. The key step for introducing the necessary functionality at C-1 involved the regio- and stereoselective cis hydroxylation of enol ether **37b** with osmium tetraoxide in the presence of *tert*-butyl hydroperoxide.

Much recent effort has been devoted to developing new biorational methods for insect control. In this context, the application of natural antifeedants is of potential value due to their specificity of action and their nontoxic character. Naturally occurring antifeedants include glycosides of steroidal alkaloids,[1] aromatic steroids,[2] quinones,[2d,3] germacrane sesquiterpenes,[4] clerodanes,[5] and iridoids.[6] A series of "drimane" sesquiterpenes, isolated from the bark of the East African plants *Warburgia ugandensis* and *W. stuhlmanii* (Canellaceae), i.e., muzigadial[7a,b] (**1a**), warburganal[7c] (**2**), polygodial[7d] (**3**), and ugandensidial[7e] (cinnamodial,[7f] **4**) have shown highly potent antifeedant activity against the African army worms *Spodoptera littoralis* and *S. exempta*. In addition, compounds **1a** and **2** exhibit a broad antibiotic spectrum, as well as helicocidal activity against the schistosome-transmitting snails *Biomphalaria glabratus*, *B. pfeifferi* (LD_{50} = 5 ppm within 24 h), and *Lymnaca natalensis* (LD_{50} = 10 ppm within 24 h).[7a]



1a: αOH, βCHO
1b: βOH, αCHO
2
3
4

Total syntheses of warburganal (**2**) and polygodial (**3**) have been accomplished by several groups, starting from 2,6,6-trimethyl-1-vinylcyclohex-1-ene,[8a-c] isodrimenin,[8d] 1-abietic acid,[8e] or 5,5,9-trimethyl-*trans*-1-decalone[8f,g] or through an ingenious metathesis/transannular ene sequence to the required trans-fused decalin derivative.[8h] On the other hand, to our knowledge, the synthesis of muzigadial has not been heretofore reported in the literature. Nevertheless, **1a** clearly provides a challenging target to synthetic organic chemists, since it possesses an exomethylene group at C-5 and the chiral center at C-6 not found in warburganal. To avoid confusion and allow direct comparison between spectral and stereochemical data, the numbering system of muzigadial has been used throughout the discussion. One plausible retrosynthetic analysis of **1a** would require dialdehyde **33**, which we hoped would

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