Steroidal Adducts. V.[1] Further Studies of the Reactions of Steroidal Dienes with Tetracyanoethylene

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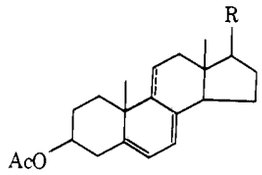
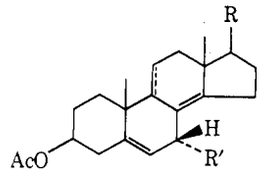
Two new compounds from reactions of ergosteryl acetate 1 with tetracyanoethylene are assigned structures 8 and 9 from analytical and spectral data. Mass spectra of the reaction products are described. Reactions in this series are considered in the light of steric effects on ene and Diels–Alder reactions.

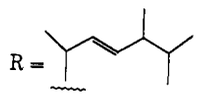
In a recent paper of this series,[4] some reactions of tetracyanoethylene with ergosteryl acetate (1), 9(11)-dehydroergosteryl acetate 2, and related steroids were described. While the chief products from compounds 1 and 2 were the ene adducts 3 and 4, both were accompanied, for the 9(11)-dehydro compound to a major extent, by the dehydrogenated adduct 5. Compound 5 was also produced by mild thermal decomposition of 4 in the presence of tetracyanoethylene. This compound was suggested to arise from an intermediate pentaene 6, whose origin from 4 was inferred from the isolation of tetracyanoethane from the reaction and by trapping 6 as its maleic anhydride adduct 7. The formation of 5 from 2, then, involves dehydrogenation *via* ene-adduct decomposition, and its origin from 1 requires two dehydrogenation steps.

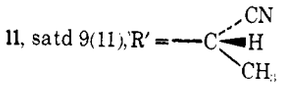


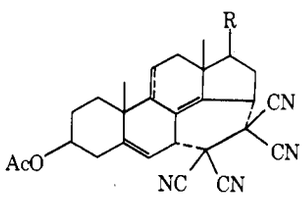
1, satd 9(11)
2, Δ 9(11)



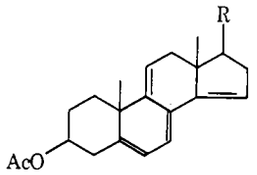
3, satd 9(11), R′ = —C(CN)$_2$CH(CN)$_2$
4, Δ 9(11), R′ = —C(CN)$_2$CH(CN)$_2$







5, Δ 9,11
8, satd 9(11)



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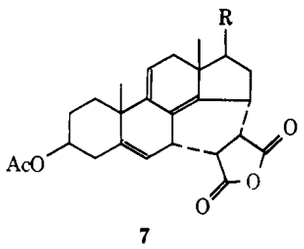
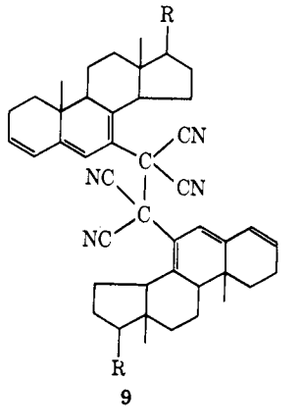


7

We now report the isolation of two further new compounds from reaction mixtures of ergosteryl acetate 1 and tetracyanoethylene, discuss spectral properties of the adducts, consider the role of steric effects in these reactions, and suggest a pathway for the formation of 5 from 1.

Adduct 5 was formed in best yield when the ene adduct 4 was placed in chloroform–nitromethane at 0° in contact with additional tetracyanoethylene. We therefore attempted to prepare the analogous compound 8 from 3 under the same conditions. However, no 8 was thus obtained from 3, but, when ergosteryl acetate 1 was treated with 2 equiv of tetracyanoethylene under much more vigorous conditions (benzene at 75°), two new crystalline products, accompanied by extensive decomposition, were obtained. The first analyzed for $(C_{31}H_{41}N_2)_n$, and had $[\alpha]D$ + 140°. Its uv spectrum showed λ_{max} 306, 313 nm (ε 53,000, 48,000), which is reasonably consistent with a $\Delta^{3,5,7}$ triene.[5] The nmr spectrum showed three vinyl protons per steroid nucleus in addition to those of the side chain, two of them as an AB quartet. Although it is not certain that the material is completely homogeneous (separation of mixed isomeric bis steroids is frequently difficult), the data available are consistent with the compound 9, $C_{62}H_{82}N_4$, being a major component of the material, yet with some isomeric octaenes probably present as well. Repeated attempts to observe a molecular ion in the mass spectrum of the compound were unsuccessful, the highest peak observed being at *m/e* 504, corresponding to a species such as 10. The close relationship of the new compound to adduct 3 was emphasized by its formation when 3 was heated alone in methanol, benzene, acetic acid, chloroform–nitromethane, or ether. Structure 9 can be envisaged



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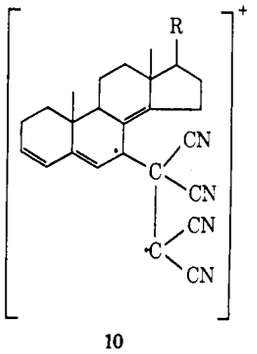

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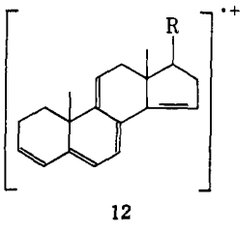
(1) Part IV: D. E. Burke and P. W. Le Quesne, *J. Org. Chem.*, **36**, 2397 (1971).
(2) Kent State University.
(3) University of Michigan; to whom inquiries should be addressed.
(4) A. L. Andrews, R. C. Fort, Jr., and P. W. Le Quesne, *J. Org. Chem.*, **36**, 83 (1971).
(5) L. F. Fieser and M. Fieser, "Steroids," Reinhold, New York, N. Y., 1959, p 17.

as arising from two molecules of **3** by radical cleavage and combination reactions, elimination of two molecules of acetic acid, and double-bond shifts.

The second new compound was the desired adduct **8**. It was obtained together with **5**, which it closely resembles in physical properties. Separation of these compounds also was difficult, but repeated crystallization gave samples of **8** contaminated with ~10% of **5**. This estimate was made from consideration of uv, nmr, and mass spectral data (see below). This material had $[\alpha]D$ −223°. The uv spectrum of **8** had λ_{max} 220, 284 nm (ϵ 4655, 504), which is in accord with that of **3** [λ_{max} 213 nm (ϵ 8080)] contaminated with a little **5** [λ_{max} 284 nm (ϵ 8550)].[4] The nmr spectrum of **8** showed the three vinyl protons as two multiplets, one at τ 4.4, integrating for slightly more than one proton owing to the superposition of the corresponding 2 H signal from **5**,[4] and the other from the two side-chain protons, at ~τ 4.7. The eight methine protons of **8** appear upfield from the vinyl protons in three groups: τ 5.3 (1 H, m, C-3α), 6.8 (2 H, m, C-7β and C-15β), and in a group of twelve protons between τ 7.0 and 8.0 which also contains the acetate methyl group at τ 7.98 and the two allylic ring methylene protons at C-4. The ten nonallylic ring methylene protons fall between τ 7.98 and 8.78. The C-18 and C-19 signals of **8** appear as superimposed signals at τ 9.1. This is in accord with τ 9.05 found for **3**[4] and τ 9.1 reported for **11**,[6] and reaffirms the presence of a $\Delta^{5,8(14)}$-diene system.

Strong confirmation of structure **8** comes from comparison of its mass spectrum with those of **5** and related steroids. On electron impact adduct **5** undergoes retro Diels–Alder loss of tetracyanoethylene and elimination of acetic acid to give a peak at *m/e* 374. An apparently identical fragment is found (as the base peak) in the spectrum of the ene adduct **4** in which the molecular ion loses acetic acid and tetracyanoethane, giving an ion of probable structure **12**. The formation of **12** on electron impact from **4** is analogous to the ground state dehydrogenation mentioned above. Subsequent decomposition of ion **12** is the same in



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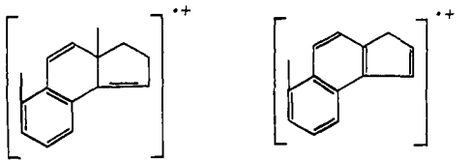
both cases; the side chain (*m/e* 125) is lost giving an ion at *m/e* 249, which is analogous to ions at *m/e* 253 and 251 in the spectra of ergosteryl acetate **1** and 9(11)-dehydroergosteryl acetate **2**, respectively. Loss of methane (C-19) follows to give an ion at *m/e* 233, or butadiene from ring A to give ion **13** at *m/e* 195, which loses methane to give ion **14** at *m/e* 179.

Similarly, on electron impact both **8**, by retro Diels–Alder loss of tetracyanoethylene and elimination of acetic acid, and **3**, by loss of tetracyanoethane and acetic acid, give a base peak at *m/e* 376. This ion then produces the same fragmentation pattern in both



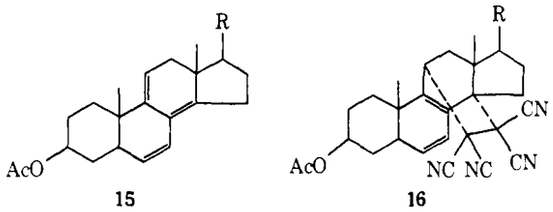
13 **14**

these spectra, and this pattern is the same, except that the peaks are at 2 mass units higher, as that from the *m/e* 374 ion from **5** and **4**. This strikingly confirms the analogous structures of **5** and **8**.

In the spectra of **3** and **4** the peaks corresponding to the loss of tetracyanoethane (*m/e* 376 for **3** and 374 for **4**) are accompanied by peaks at *m/e* 378 and 376, 18 and 9%, respectively, the intensities of the former. Since the peak at *m/e* 378 in ergosteryl acetate, which corresponds to the loss of acetic acid, was accompanied under analogous conditions on our instrument by a peak at *m/e* 380 of 7% its intensity, we believe that the *m/e* 376 and 378 peaks from **4** and **3** arise, in part at least, from retro ene reactions, analogous to the McLafferty rearrangement, as adumbrated previously.[4] Predominantly, however, the ene adducts on electron impact characteristically lose tetracyanoethane and the Diels–Alder adducts (*e.g.*, **5**, **8**, and **16**) tetracyanoethylene.

These mass spectra are similar to that of ergosteryl acetate **1** which strongly resembles the spectrum of ergosterol itself.[7-9] The steroid 9(11)-dehydroergosteryl acetate (**2**) on electron impact shows, because of the 9(11) double bond, much reduced ring-C cleavage compared with that in ergosteryl acetate **1**, which therefore reduces the abundance of ring A–B fragments at *m/e* 158, 143, and 128. The ions representing loss of acetic acid, angular methyl groups, and side chain are analogous but of two mass units less.

The mass spectrum of 3β-acetoxyergosta-6,8(14),-9(11),22-tetraene (**15**) and its Diels–Alder adduct **16**



15 **16**

are very similar. Both, as expected,[10,11] lose acetic acid less readily than the Δ^5 steroids discussed above, and a metastable ion at *m/e* 202.6 documents the loss of acetic acid after the loss of side chain or side chain plus tetracyanoethylene. The prominent ion **17** at *m/e* 311 readily loses methane with aromatization of ring C, to give an ion at *m/e* 295; the ion resulting from loss of acetic acid from **17** itself loses ring A (butadiene) or methane from C-18 to give ions at *m/e* 197 and 235. A strong tendency to cleavage in ring B is

(6) D. N. Jones, P. F. Greenhalgh, and I. Thomas, *Tetrahedron*, **24**, 5215 (1968).

(7) S. S. Friedland, G. H. Lane, Jr., R. T. Longman, K. E. Train, and M. J. O'Neil, Jr., *Anal. Chem.*, **31**, 169 (1959).

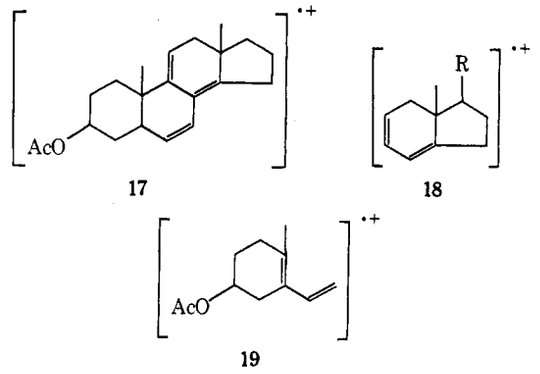
(8) J. Jaurégiberry, J. H. Law, J. A. McCloskey, and E. Lederer, *Biochemistry*, **4**, 347 (1965).

(9) F. R. Smith and E. D. Korn, *J. Lipid Res.*, **9**, 405 (1968).

(10) G. Galli and S. Maroni, *Steroids*, **10**, 189 (1967).

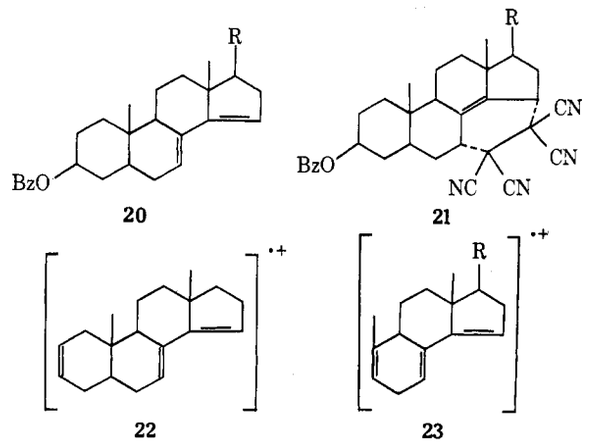
(11) H. J. M. Fitches in "Advances in Mass Spectrometry," Vol. 2, R. M. Elliot, Ed., Pergamon Press, New York, N. Y., 1963, p 428.

evinced by fission of the tetraene molecular ion into fragments **18** (*m/e* 257) and **19** (*m/e* 179).



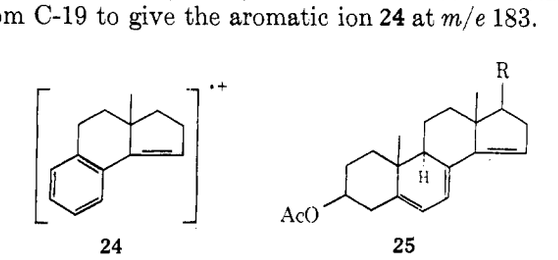
17 18 19

The steroid 3β-benzoyloxyergosta-7,14,22-triene (**20**) and its Diels–Alder adduct **21** also show virtually identical behavior on electron impact. In analogy to the



20 21 22 23

compounds above, benzoic acid is not lost readily owing to the absence of a Δ^5 double bond. The ion **22** (*m/e* 253), resulting after loss of benzoic acid and the side chain, undergoes loss of methane (probably C-18) to give an ion at *m/e* 237, or butadiene from ring A to ion **23** at *m/e* 199, which in turn losses methane from C-19 to give the aromatic ion **24** at *m/e* 183. Al-



24 25

though one must be cautions in attributing unique structures to polyene radical cations such as these, it seems clear that the overall patterns of fragmentation are characteristic of the locations of single or grouped alkene linkages in these compounds and are thus useful in structure determination.

The data accumulated suggest that steric factors exert major control of the reactions between steroidal alkenes and tetracyanoethylene. The fact that no Diels–Alder adduct was obtained with ergosteryl acetate or 9(11)-dehydroergosteryl acetate suggests that tetracyanoethylene is too bulky to achieve the required transition state geometry. The literature of steroid addition reactions of this kind[12] shows that all nonacetylenic dienophiles giving Diels–Alder adducts with $\Delta^{5,7}$ and $\Delta^{5,7,9(11)}$ steroids possess cis vinyl hydrogens or a cis diazo function. The bulk of cis vinyl nitrile groups is, from molecular models, great enough that the approach of tetracyanoethylene to **1** to give a Diels–Alder adduct is hindered not only by the 9α hydrogen but by the 1α and 12α hydrogens as well. That **1** does not give a $\Delta^{8,9}$ ene adduct isomeric with **3** is probably also a consequence of the bulk of the nitrile groups; the transition state for this reaction is appreciably hindered by the 15α hydrogen (*cf.* ref 6). (Steric effects, however, are not the only factors in all reactions of this kind; the difference in reactivity of benzyne and tetrafluorobenzyne with the $\Delta^{5,7}$ diene system[13] is of interest here.)

For steric reasons too, the decomposition of the 7α-tetracyanoethyl ene adducts to tetracyanoethane and a dehydrogenated steroid preferentially involves the accessible 15α hydrogen. The formation of **5** in minute yield from **1** and tetracyanoethylene could involve initial decomposition of **3** to give 3β-acetoxyergosta-5,7,14,22-tetraene (**25**) which, if not trapped as **8**, might, lacking the 15α hydrogen, undergo an ene reaction involving the 9α hydrogen, dehydrogenation at the 9(11) bond, and final trapping as **5**.

Further work on steric aspects of these reactions and on the dehydrogenations is in progress.

Experimental Section

General experimental directions are as for ref 4.

3β-Acetoxy-7α,15α-tetracyanoethanoergosta-5,8(14),22-triene (8) and the Bis Steroid 9.—Ergosteryl acetate (**1**) (13.6 g, 0.031 mol) and tetracyanoethylene (8.0 g, 0.062 mol) were held in benzene solution at 75° for 2.5 hr. The dark solution was filtered, giving tetracyanoethane (1.6 g, 0.012 mol), identified by comparison with authentic material. Addition of heptane precipitated slightly impure tetracyanoethylene (1.9 g), identified by its melting point, ir spectrum, and orange color reaction with xylene. Replacement of chloroform by ether gave fine white crystals of the bis steroid **9**, recrystallized for analysis from benzene–ethyl acetate: mp 198° with prior sintering, giving a red melt; vacuum mp 202°; $[\alpha]^{20}D$ +140° (*c* 1.0, $CHCl_3$); uv $\lambda_{max}^{CHCl_3}$ 306, 313 nm (ε 53,000, 48,000); nmr τ 3.56, 3.73, 3.95, 4.10 (4 H, AB q, *J* = 10 Hz, vinyl H's) 4.47 (2 H, m, vinyl H), 4.80–5.70 (4 H, m, C-22,23 H's), 6.32–6.85 (2 H, m). *Anal.* Calcd for $(C_{31}H_{41}N_2)_2$: C, 84.30; H, 9.35; N, 6.34. Found: C, 84.08, 84.19; H, 9.37, 9.46; N, 6.28, 6.35. Mass spectrum: *m/e* (rel intensity) 504 (0.3), 479 (1.5), 376 (100), 361 (14), 251 (94), 236 (15), 235 (12), 209 (8), 197 (32), 155 (19), 143 (10), 128 (7). Addition of heptane to the ether mother liquor caused precipitation of impure **8** (2.5 g, mp 160–180°), contaminated with **5**. Two careful recrystallizations from benzene–heptane and two from ethyl acetate gave the analytical sample of substantially pure **8** (0.53 g): mp 195–196° (melt cooling to a yellow solid); $[\alpha]^{20}D$ −223° (*c* 1.0, $CHCl_3$); uv $\lambda_{max}^{cyclohexane}$ 220, 284 nm (ε 4655, 504); nmr τ 4.37 (>1 H, m, C-6 H), 4.72 (2 H, m, C-22,23 H's), 5.30 (1 H, m, C-3α H), 6.75 (2 H, m, C7β,15β H's), 7.0–7.9 (5 H, m, C-9,17,20,24,25 H's), 7.97 (3 H, s, CH_3-COO–, 7.9–8.7 (12 H, m, ring $-CH_2$'s), 9.10 (3 H, s, probably C-18), 9.07 (3 H, s, probably C-19). *Anal.* Calcd for $C_{36}H_{44}N_4O_2$: C, 76,56; H, 7.85; N, 9.92. Found: C, 76.66; H, 7.78; N, 9.82.

Gentle reflux of adduct **3** (360 mg) in methanol (7 ml) for 1 hr gave a yellow suspension from which colorless needles of **9** (68 mg) identical with that obtained above, were filtered off. Replacement of the methanol solvent by benzene, acetic acid, chloro-

(12) For a summary see A. L. Andrews, Ph.D. Thesis, Kent State University, 1971, p 12.

(13) I. F. Eckhard, H. Heaney, and B. A. Marples, *J. Chem. Soc. C*, 2098 (1969).

form–nitromethane, or ether gave the same result. Mass spectral data in *m/e* (rel intensity) follow.

Compound **2**: ion chamber 143°; M^+ 436 (9), 376 (100), 361 (13), 251 (41), 235 (12), 209 (16), 197 (9), 181 (10), 158 (2), 155 (10), 143 (6), 128 (4); metastable ion 347.

Compound **3**: ion chamber 134°; 436 (7), 378 (18), 376 (100), 361 (14), 253 (12), 251 (67), 237 (9), 235 (19), 209 (12), 197 (22), 181 (12), 155 (21), 143 (13), 128 (13).

Compound **4**: ion chamber 200°; 436 (2), 434 (14), 376 (9), 374 (100), 359 (10), 249 (64), 235 (25), 233 (19), 209 (10), 207 (11), 195 (7), 179 (11).

Compound **5**: ion chamber 185°; M^+ 562 (0.3), 502 (0.6), 434 (9), 374 (100), 359 (15), 249 (60), 233 (28), 207 (18), 179 (18), 153 (4); metastable ions 165.7, 345.

Compound **8** (containing some **5**): ion chamber 200°; 504 (16), 434 (5), 376 (100), 374 (23), 36 (8), 251 (19), 249 (21), 235 (7), 233 (5), 209 (8), 207 (5), 197 (5), 195 (7), 181 (6), 179 (6), 155 (6), 153 (6); metastable ions 324, 345.

Compound **15**: ion chamber 135°; M^+ 436 (38), 376 (26), 361 (17), 311 (71), 295 (24), 257 (14), 251 (100), 235 (19), 209 (24), 197 (33), 181 (21), 155 (24), 179 (17), 119 (8), 55 (76); metastable ions 202.6, 222.

Compound **16**: ion chamber 190°; M^+ 564 (3), 504 (5.5), 436 (31), 376 (33), 361 (17), 311 (45), 295 (23), 258 (12), 251 (100), 235 (21), 209 (27), 197 (31), 181 (17), 179 (14), 155 (19), 119 (5), 55 (70); metastable ions 202.6, 222.

Compound **20**: ion chamber 180°; M^+ 500 (42), 485 (19), 375 (39), 374 (100), 363 (4), 359 (4), 253 (14), 237 (6), 211 (3), 199 (6), 183 (5), 157 (9), 55 (60); metastable ions 170.5, 222, 280, 322, 345, 471.

Compound **21**: ion chamber 220°; M^+ 628 (2), 613 (0.2), 500 (13), 485 (12), 375 (21), 374 (58), 253 (6), 237 (4), 183 (3), 157 (6), 55 (100); metastable ions 280, 471.

Registry No.—**2**, 1060-56-6; **3**, 21549-35-9; **4**, 21549-36-0; **5**, 26885-77-8; **8**, 36959-76-9; **9**, 36959-77-0; **15**, 36959-78-1; **16**, 36959-79-2; **20**, 36959-80-5; **21**, 36959-81-6; tetracyanoethylene, 670-54-2.

Acknowledgments.—We thank Mr. Jack Eyman for valuable assistance with mass spectra, and the National Science Foundation for providing funds for the mass spectrometer at Kent State University.

Stereochemistry of Some Δ^1-Butenolide Syntheses

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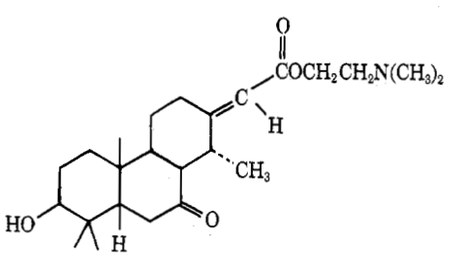
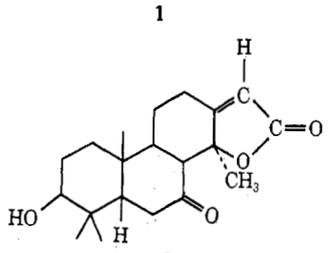
Alkylation of *trans*-1- and *trans*-2-decalone with ethyl bromoacetate *via* the pyrrolidine enamine and subsequent ester hydrolysis and dehydration (Ac_2O) gave equatorially fused butenolides. The Reformatsky products from 3(*a*)-acetoxy-*trans*-2-decalone, ethyl bromoacetate, zinc, and trimethyl borate were saponified and ring closed to give isomeric β-hydroxy γ-lactones which could be dehydrated to the axially fused butenolide. Similar reactions with 3(*e*)-acetoxy-*trans*-2-decalone gave the other two isomeric β-hydroxy-γ-lactones which on dehydration gave the equatorially fused butenolide. Stereochemical assignments were made on the basis of nmr spectra.

Interest in the preparation of conformationally rigid butenolide analogs of cassaine (**1**) such as **2** made

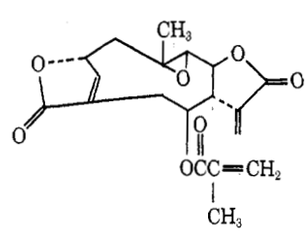


1



2

necessary the investigation of the stereochemistry of some Δ^1-butenolide syntheses. Of the large number of syntheses for the Δ^1-butenolides most have been applied only to nonfused ring systems.[2] However, in recent years several butenolide syntheses have been used for fused ring systems involved in naturally occurring compounds.[3-10] Further interest in the chemistry of butenolides has been generated by the discovery of naturally occurring fused butenolides with tumor-inhibitor activity such as elephantopin (**3**).[11]



3

The butenolide syntheses investigated were selected because they appeared to have applicability in the synthesis of the desired cassaine analogs. *trans*-Decalin was chosen as the model because it is conformationally rigid and the B–C rings of cassaine are a trans-fused decalin ring system. Thus, synthetic approaches to 2-

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