white crystals: mp 207–208°; $[\alpha]^{25}D$ +20.99 ± 1.18 (c 1.091, MeOH). The ir and nmr spectra of this material were identical with those of the natural product II.

Anal. Calcd for $C_{15}H_{18}O_6$: C, 61.27; H, 6.17. Found: C, 61.30; H, 6.01.

Alkaline Degradation of V.—A 4.1-g aliquot of V was dissolved in 200 ml of absolute EtOH, 20 g of solid KOH was added, and the mixture refluxed overnight under N_2. The cooled reaction mixture was filtered, concentrated to small volume, acidified, and extracted with ethyl acetate to get upon work-up a brown gum which was passed over 200 g of grade 62 acid-washed silica gel and eluted with 70:30 $CHCl_3$–hexane solution. Fraction volume was 80–85 ml. Fractions 3–25 were combined to give 2.5 g of a viscous oil which was a mixture and labeled fraction A. Fractions 26–38 yielded about 2.0 g of an oil which solidified. The material was recrystallized from ethyl acetate–hexane to give a first crop of 1.2 g of faintly yellow crystals which spectral data showed to be VII or 1-hydroxy-3,5-dimethoxy-4-(2′-hydroxyethyl)acetophenone: mp 133–134°; λ_{max}^{MeOH} 213 nm (ε 18,000), 230 (sh, 12,200), 290 (19,200), 330 (sh, 3600); λ_{max}^{NaOH} 215 nm (ε 36,000), 235 (sh, 18,600), 295 (6000), 330 (sh, 3300); δ ($CDCl_3$) 1.85 (1 H, exchangeable singlet) ethanolic OH, 2.60 (3 H, singlet) methyl ketone, 2.92 [2 H, triplet ($J \sim 7$ cps)] hydroxy methylene, 3.84 and 3.89 (3 H and 3 H, singlets) two aromatic methoxyls, 5.98 (1 H, singlet) aromatic H, 13.98 (1 H, exchangeable singlet) aromatic OH.

Anal. Calcd for $C_{12}H_{16}O_5$: C, 60.00; H, 6.66. Found: C, 60.38; H, 6.63.

Fraction A was again passed over silica gel. This time 90 g of acid-washed material was used and elution was carried out using a gradient of 10–50% ethyl acetate in hexane solution. Fraction size was 80–90 ml. Fractions 2–5 gave 0.6 g of residue which was recrystallized from ethyl acetate–hexane to give a first crop of 300 mg of faintly yellow crystals which were subsequently shown to be X or 1-hydroxy-3-methoxy-4,5-(2′,3′-dihydrofuro)acetophenone: mp 106–107°; λ_{max}^{MeOH} 212 nm (ε 18,700), 238 (sh, 10,400), 292 (18,500); λ_{max}^{NaOH} 214 nm (ε 38,000), 238 (sh, 15,600), 300 (6200); δ ($CDCl_3$) 2.57 (3 H, singlet) methyl ketone, 3.12 [2 H, triplet ($J \sim 7$ cps)] benzylic methylene, 3.83 (3 H, singlet) aromatic methoxyl, 4.67 [2 H, triplet ($J \sim 7$ cps)] methylene of ether linkage, 5.95 (1 H, singlet) aromatic proton, 14.00 (1 H, exchangeable singlet) phenolic proton.

Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.30; H, 5.67.

Fraction 8–16 on evaporation gave 1.0 g of a viscous oil which partially solidified. The solid was recrystallized from ethyl acetate–hexane to yield 300 mg of faintly yellow crystals, mp 97°, which spectral data showed to be IX: λ_{max}^{MeOH} 213 nm (ε 21,100), 230 (sh, 15,500), 290 (21,300), 330 (sh, 4200); λ_{max}^{NaOH} 213 nm (ε 49,000), 235 (sh, 16,900), 295 (7000), 240 (sh, 4100); ν (KBr) 1740 and 1635 cm^{-1}; δ ($CDCl_3$) 2.00 (3 H, singlet) acetyl methyl, 2.63 (3 H, singlet) aryl methyl ketone, 2.95 [2 H, triplet ($J \sim 7$ cps)] benzylic methylene, 3.90 and 3.92 (3 H and 3 H, singlets) aromatic methoxyls, 4.20 [2 H, triplet ($J \sim 7$ cps)] acetoxy methylene, 5.98 (1 H, singlet) aromatic proton, 13.93 (1 H, singlet) chelated phenolic proton.

Anal. Calcd for $C_{14}H_{18}O_6$: C, 59.56; H, 6.43. Found: C, 59.26; H, 6.36.

Work-up of fractions 27–37 yielded 250 mg of VII.

Alkaline Degradation of III.—About 0.4 g of III was dissolved in 25 ml of EtOH, 3 g of KOH was added, and the mixture was refluxed overnight under N_2. The solvent was evaporated and the mixture acidified with 4 *N* HCl and then extracted with ethyl acetate. Work-up of the ethyl acetate extract gave 270 mg of yellow solids which were passed over 18 g of acid-washed grade 62 silica gel and eluted with 5% ethyl acetate in hexane. The second holdback volume yielded 200 mg of material which upon recrystallization gave 110 mg of X, mp 107–108°.

Preparation of VIII.—About 1.2 g of VII was stirred overnight in 200 ml of $CHCl_3$ with 15 g of Ag_2O and 20 ml of CH_3I. The reaction mixture was filtered and the solvent evaporated to get 1.2 g of solid material which was passed over 90 g of acid-washed grade 62 silica gel and eluted with a gradient of 5–20% ethyl acetate in hexane. Fraction size was 80–85 ml. Fractions 9–12 gave 0.7 g of crystals which were recrystallized to give a first crop of 320 mg, mp 94–94.5°, which spectral data showed to be VIII: λ_{max}^{MeOH} 213 nm (ε 18,000), 230 (sh, 12,700), 287 (20,300), 330 (sh, 3800); δ ($CDCl_3$) 2.62 (3 H, singlet) methyl ketone, 2.93 [2 H, split triplet ($J \sim 7$ cps)] benzylic methylene, 3.37 (3 H, singlet) aliphatic methoxyl, 3.48 [2 H, split triplet ($J \sim 7$ cps)] $-OCH_2$, 3.90 (6 H, singlet) 2 aromatic methoxyls, 5.98 (1 H, singlet) aromatic proton, 13.93 (1 H, singlet) chelated phenolic proton.

Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.52; H, 7.14. Found: C, 61.40; H, 7.06.

Registry No.—I, 34288-33-0; II, 34288-34-1; III, 34288-35-2; IV, 34288-36-3; V, 34288-37-4; VI, 34288-38-5; VII, 34288-73-8; VIII, 34288-74-9; IX, 34288-75-0; X, 34288-76-1; phlaroglucinol, 108-73-6.

Acknowledgment.—We wish to thank our colleagues for their assistance, in particular, Dr. H. Tresner and Miss Jean Hayes for culture isolation and identification, Mr. A. J. Shay for large-scale fermentation, Mr. Murray Dann for large-scale work-ups, Mr. L. Brancone for microanalytical data, Mr. W. Fulmor for spectral data and optical rotations, and Miss Pat Mullen of Cyanamid Stamford Laboratories for the CD curve.

Chemical Modifications of Zearalenone. I

N. P. JENSEN,* R. D. BROWN, S. M. SCHMITT, T. B. WINDHOLZ, AND A. A. PATCHETT

Department of Synthetic Chemical Research, Merck Sharp & Dohme Research Laboratories, Rahway, New Jersey 07065

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Chemical transformations of the aliphatic portion of the mold metabolite zearalenone were examined. Reactions at the C′-6 ketone and the C′-1 double bond and positions adjacent to these reaction centers are reported. The reactions proved to be quite regioselective.

The mold metabolite zearalenone (1),[1] which has shown hormonal and growth-promotant activities,[1a] has previously been synthesized,[2] its absolute configuration has been determined,[3] and modifications in the aromatic ring with the resulting changes in biological activity have been reported.[4] In this report some transformations of the lactone ring are examined. Although one might expect a 14-member ring to have several conformations of relatively equal energies, we

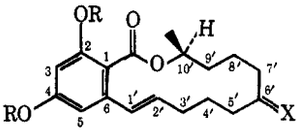
(1) (a) M. Stab, R. S. Baldwin, J. Tuite, F. N. Andrews, and K. G. Gillette, *Nature (London)*, **196**, 1318 (1962); (b) W. H. Urry, H. L. Wehrmeister, E. B. Hodge, and P. H. Hidy, *Tetrahedron Lett.*, 3109 (1966); (c) zearalenone used in these experiments was supplied by Commercial Solvents Corp.

(2) (a) D. Taub, N. N. Girotra, R. D. Hoffsommer, C. H. Kuo, H. L. Slates, S. Weber, and N. L. Wendler, *Tetrahedron*, **24**, 2443 (1968); (b) I. Vlattas, I. T. Harrison, L. Tökes, J. H. Fried, and A. D. Cross, *J. Org. Chem.*, **33**, 4176 (1968).

(3) C. H. Kuo, D. Taub, R. D. Hoffsommer, N. L. Wendler, W. H. Urry, and G. Mullenback, *Chem. Commun.*, 761 (1967).

(4) D. B. R. Johnston, C. A. Sawicki, T. B. Windholz, and A. A. Patchett, *J. Med. Chem.*, **13**, 941 (1970).

were gratified to find that various reactions showed selectivities indicative of definitely preferred conformations. It should be noted that cyclization to dideoxyzearalane, which lacks zearalenone's double bond, ketone, and aromatic hydroxyls, has been reported to be difficult,[5] and hence typical of rings in the 7- to 13-member class,[6] while formation of the lactone in dimethoxyzearalenone under less dilute conditions has been achieved in as high as 80% yield.[2a] This comparison demonstrates the importance of the additional functional groups in conferring preferred conformations in zearalenone and its derivatives.



1, R = H; X = O

2, R = H; X = 

3, R = CH_3; X = O

4, R = CH_2Ph; X = O

5, R = CH_2OCH_3; X = O

6, R = CH_2OCH_3; X = 

7, R = CH_2OCH_3; X = 

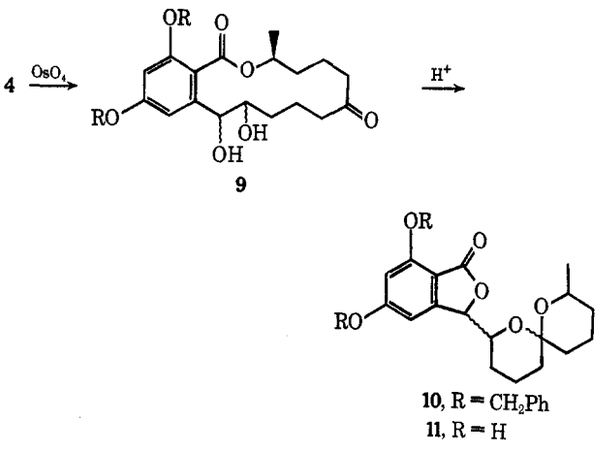
8, R = CH_2OCH_3; X = 

In order to effect reactions on the aliphatic portion of zearalenone, various groups were used to block the aromatic hydroxyls. Besides the use of a methyl group, which was used in the syntheses of zearalenone,[2] benzyl and methoxymethyl groups were used. The benzyl groups were used if the concomitant double bond reduction on hydrogenolytic removal was acceptable. If retention of the double bond was desired a methoxymethyl group was used. We found that a combination of *p*-toluenesulfonic acid, water, and ethylene glycol in refluxing benzene cleanly removed this group as well as a 6′ ketal protecting group. This is demonstrated in the conversion of **15** to **16** and **12** to **13**.

The 1′,2′ trans double bond of zearalenone appears to be quite electron poor. Exposure of **3** to either perphthalic or *m*-chloroperbenzoic acid in chloroform solution for 2 weeks gave no significant reaction. This is in accord with the general observation that a *m*-methoxy substituent has no electron-supplying or electron-withdrawing effect.[7] It is therefore the electron-withdrawing inductive effect of the *o*-carboxy group which is the important factor in the electron availability of the double bond.

The more reactive reagent osmium tetroxide reacted smoothly with the double bond of **4** to give a diol mixture **9** (R = CH_2Ph) which was not fully characterized owing to the great ease with which it rearranged to the isomeric mixture **10** in the presence of acid[8] (Scheme I). While this is an unusual rearrangement in that one ring-opening and three ring-forming reactions take place, all the elements of this transformation

SCHEME I



9

10, R = CH_2Ph

11, R = H

have already been demonstrated in similar molecules and the 1,6 nature of the ketone and lactone alcohol has been used as a means of protecting these functions in the synthesis of zearalenone.[2a]

Hydroboration of the double bond was also sluggish and was complicated by formation of products (**14**) identified as phthalides by the 5.71-μ carbonyl frequency in their infrared spectrum. In this case, it was found that phthalide formation could be reduced by running the reaction at lower concentrations. As in the case of other benzylic boranes[7] oxidation had to be run at low temperatures to avoid hydrolysis. Since a 1′ alcohol had already been found to be acid-labile, the product from hydrogen peroxide oxidation of the borane was converted immediately to ketone **12** by Sarett oxidation.[9] The product was then purified by chromatography in order to remove starting material (**6**) and phthalides (**14**) and to see if any 2′ ketone could be detected. Although no 2′ ketone was found[10] an interesting side product (**15**) of Sarett oxidation was identified (Scheme II).

The minor product **15** was thought to arise from allylic oxidation of unreacted starting material **6**. This hypothesis proved correct inasmuch as exposure of **6** to excess Sarett reagent for 2 days gave a good yield of **15**. Although chromic acid has long been used as an allylic oxidant,[11] until recently chromium trioxide in pyridine had not been generally considered a reagent for allylic oxidation. While allylic oxidation with Sarett reagent is slow compared to the oxidation of an alcohol, it can be a useful preparative reaction.[12] In the case of zearalenone, allylic oxidation with Sarett reagent was very sensitive to changes at C-6′. The compound **5** in which the C-6′ ketal is replaced with a ketone was 85% unreacted under the conditions which give an 85% yield of **15** from **6**. A likely explanation for this difference is that an sp^3 instead of an sp^2 center at C-6′ allows a more active

(5) H. L. Wehrmeister and D. E. Robertson, *J. Org. Chem.*, **33**, 4173 (1968).

(6) *Cf.* (a) K. Ziegler and R. Aurnhammer, *Justus Liebigs Ann. Chem.*, **513**, 43 (1933); (b) N. J. Leonard and C. W. Schimelpfenig, Jr., *J. Org. Chem.*, **23**, 1708 (1958).

(7) H. C. Brown and R. L. Sharp, *J. Amer. Chem. Soc.*, **88**, 5851 (1966).

(8) This rearrangement was first noted when the diol mixture was dissolved in deuteriochloroform for examination by nmr.

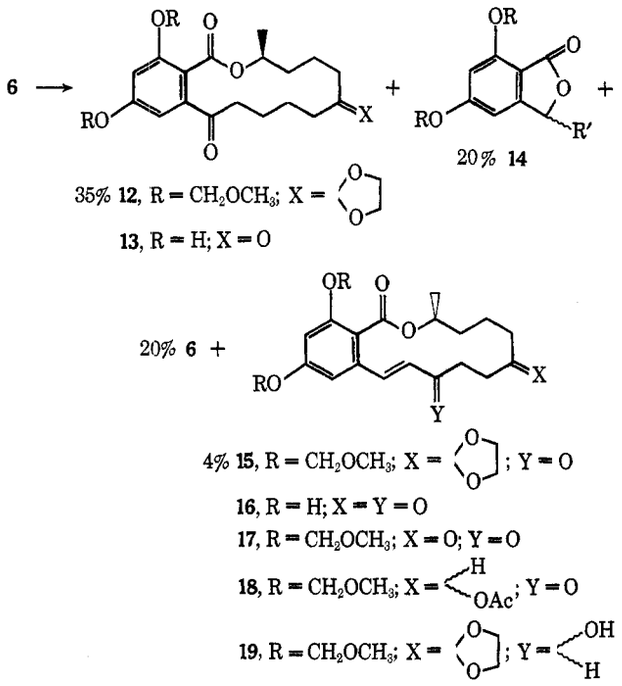
(9) (a) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Amer. Chem. Soc.*, **75**, 422 (1953); (b) J. R. Holem, *J. Org. Chem.*, **26**, 4814 (1961).

(10) H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.*, **82**, 4708 (1960), find that β-methylstyrene gives 15% of 2′ product.

(11) (a) F. C. Whitmore and G. W. Pedlow, Jr., *ibid.*, **63**, 758 (1941); (b) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, p 94.

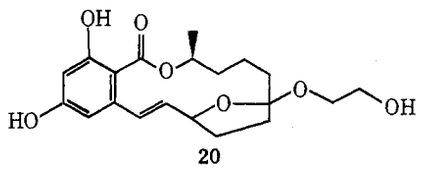
(12) Subsequent to this work it has been shown that the Collins modification of chromium trioxide–pyridine oxidation [J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968)] is an effective allylic oxidant [W. G. Dauben, M. Lorber, and D. S. Fullerton, *J. Org. Chem.*, **34**, 3587 (1969)].

SCHEME II



ring conformation to exist. When the epimeric acetate **8**, which also has an sp^3 center at C-6′, was submitted to the Sarett oxidation conditions, a good yield of a product of allylic oxidation (**18**) was again obtained.

An alternative or additional explanation for the favorable reactivity of **6** and **8** is that an sp^3 oxygen attached to C-6′ assists attack at C-3′. The fact that such oxygens at C-3′ and C-6′ can be in proximity to each other is attested to by the formation of **20**, which was prepared by reduction of **15** with $NaBH_4$ to give **19** followed by attempted simultaneous cleavage of the methoxymethyl and ketal protecting groups. Although the combination of ethylene glycol, water, and *p*-toluenesulfonic acid was found to be very good for removing these groups from **12** and **15**, in the case of **19** the tetrahydrofuran **20** was formed.[13] The structure



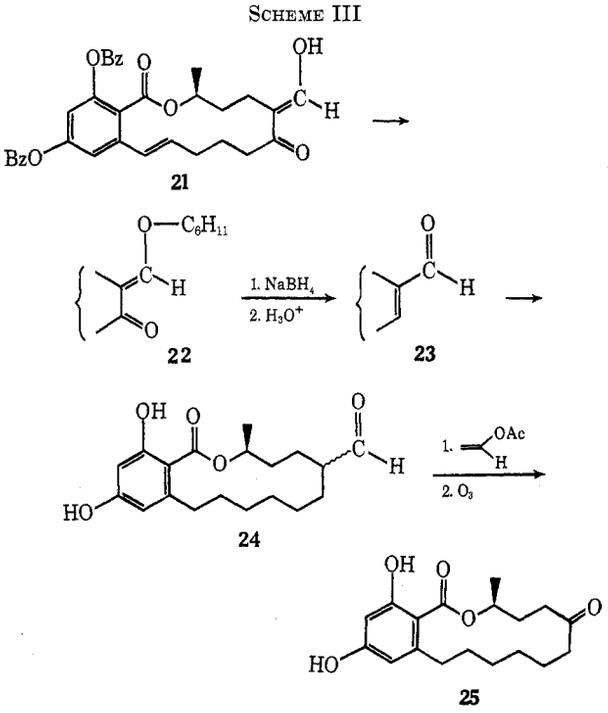
20

of this compound is based on its mass spectrum and analysis as well as the nmr of its triacetate,[14] which distinguishes it from other structure possibilities which do not have primary alcohols.

Reactions of the 6′-keto group of zearalenone were also environment sensitive. Although the α positions of this ketone are both secondary, it was found that reactions at this center showed considerable "regioselectivity."[15] One of the most useful reactions which displayed this regioselectivity was formylation in benzene using sodium hydride and *tert*-butyl alcohol as a base. Although the intermediate hydroxymethylene products of this reaction were not very stable and were therefore not characterized, isomer ratios could easily be determined by tlc and it was subsequently established (see below) that the C-7′ product (**21**) was the major isomer by a 8:1 margin.[16] Whether this selectivity is kinetic or thermodynamic has not been proven. Under the conditions of sodium ethoxide–ethanol, which are reported to be equilibrium conditions for hydroxymethylene formation,[17] the product was not stable with respect to starting ketone.

The predominance of C-7′ isomer in hydroxymethylene formation provided a starting point for the synthesis of the C-7′ ketone isomer of zearalanone. The synthetic objective of moving a ketone to an α carbon is a common one for which there are a variety of schemes.[18] In this instance the double bond was eliminated to permit the use of ozone. The attractiveness of this route (see Scheme III) lay in its utilization

SCHEME III



of the hydroxymethylene derivative and in the unambiguous course of the acid rearrangement step. This allylic rearrangement of proven course[19] has been used in diterpene synthesis.[20] Hydrogenation of **23** was accompanied by some reduction of the aldehyde **24**,[21] but it was found that purification by chromatog-

(13) The inability to hydrolyze a six-membered ether in a zearalenone derivative under acid conditions has been reported in ref 2b.

(14) We wish to acknowledge Dr. B. Arison's invaluable help and suggestions regarding nmr spectra.

(15) A. Hassner, *J. Org. Chem.*, **33**, 2684 (1968).

(16) The product ratio, while always greatly favoring the C-7′ isomer, was somewhat capricious. In one larger scale preparation only the C-7′ isomer could be detected.

(17) (a) L. M. Roch and N. Boulay, *C. R. Acad. Sci.*, **253**, 2375 (1961); (b) L. M. Roch, *Ann. Chim. (Paris)*, **6**, 105 (1961); (c) R. O. Clinton, R. L. Clark, F. W. Stonner, A. J. Manson, K. F. Jennings, and D. K. Phillips, *J. Org. Chem.*, **27**, 2800 (1962).

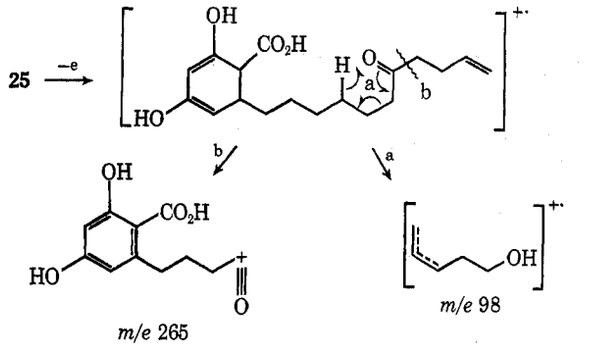
(18) *Cf.* (a) J. A. Marshall and H. Roebke, *J. Org. Chem.*, **34**, 4188 (1969); (b) A. Hassner, J. M. Larkin, and J. E. Dowd, *ibid.*, **33**, 1733 (1968); (c) G. Just and Y. C. Lin, *Chem. Commun.*, 1350 (1968).

(19) M. Stiles and A. Lonroy, *Tetrahedron Lett.*, 337 (1961); *J. Org. Chem.*, **32**, 1095 (1967).

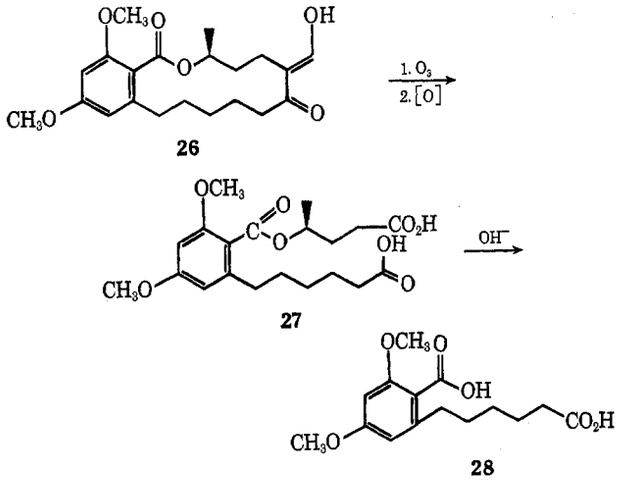
(20) R. E. Ireland and P. W. Schiess, *J. Org. Chem.*, **28**, 6 (1963).

(21) The aldehyde **24** showed increased hormonal activity [J. R. Brooks, S. L. Steelman and D. J. Patanelli, *Proc. Soc. Exp. Biol. Med.*, **137**, 101 (1971)]. This epimeric mixture (**24**) of aldehydes was separated by fractional recrystallization from benzene and epimeric purity was confirmed by nmr (see Experimental Section).

SCHEME IV



SCHEME V



raphy gave better yields than protecting the aldehyde *via* a ketal.[22]

The position of the ketone in 7′-ketozearalane (**25**) is easily seen by comparing its mass spectrum with that of its isomer zearalanone.[23a] The mass spectra of these two isomers have essentially the same peaks with the exception of two strong sets of homologous peaks.[23b] The 7′-keto compound has peaks at *m/e* 265 and 98, while zearalanone has corresponding peaks at *m/e* 251 and 112.[24] These peaks can be seen to arise from a McLafferty rearrangement at the lactone followed by α cleavage or a McLafferty rearrangement at the ketone (Scheme IV shows these cleavages for the 7′-keto isomer). Peaks at *m/e* 237 and 126 which would arise from a 5′-keto isomer are negligible in the spectrum of zearalanone and the 7′-keto isomer.

This preference for C-7′ formylation was also seen in a saturated series. Zearalanone bismethyl ether gave a 3:1 ratio of products which, while not characterized by analysis, could easily be separated by preparative tlc. The major isomer **26** thus purified was degraded *via* Scheme V to the known acid **28**,[1b] thus proving **26** to be the 7′ isomer.[25]

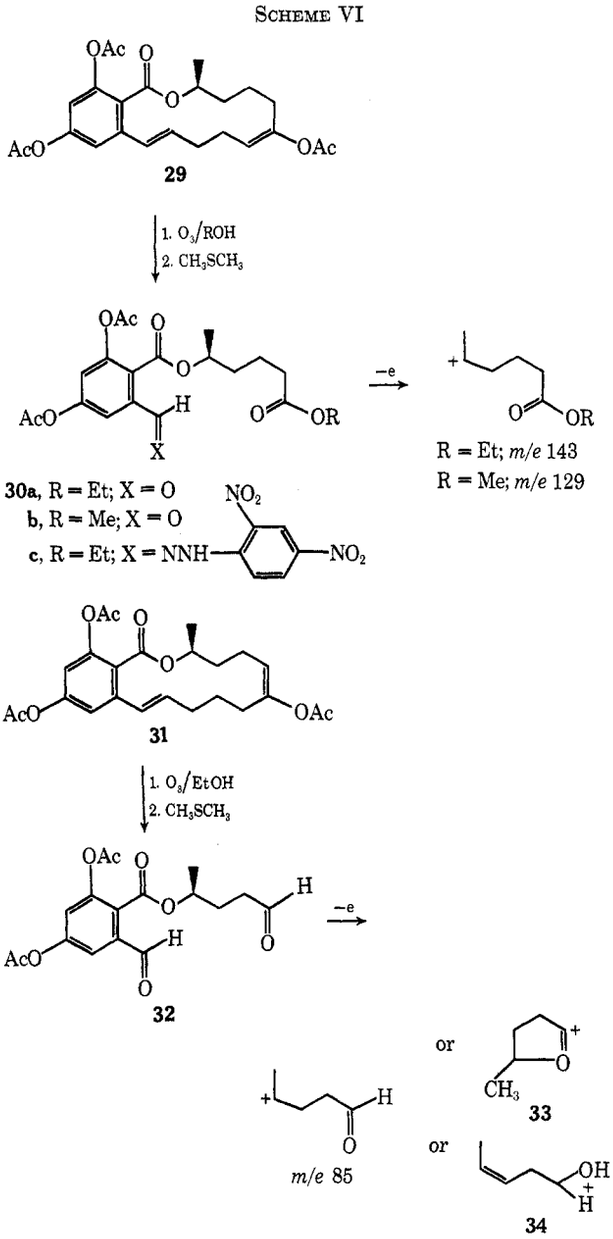
(22) This general scheme was reported in the synthesis of samandarone: S. Hara and K. Oka, *J. Amer. Chem. Soc.*, **89**, 1041 (1967).

(23) (a) We wish to thank Dr. G. Albers-Schonberg for determining and discussing with us the mass spectra reported in this paper. (b) The mass spectrum of zearalanone (see ref 1b for preparation) is given for comparison: *m/e* (rel intensity) 320 (82), 302 (59), 251 (53), 177 (35), 163 (100), 150 (40), 125 (88), 124 (26), 123 (27), 112 (86), 69 (401), 55 (65), 41 (70).

(24) This peak has been identified as coming from the aliphatic portion of zearalenone (see ref 1b).

(25) It should be noted that dimethylzearalenone preferentially gave the 7′-hydroxymethylene derivative by a ratio of 5:1 and that the relationship between saturated and unsaturated series was shown by interrelation of their pyrazole derivatives: T. B. Windholz and R. B. Brown, unpublished.

SCHEME VI



A reaction that showed even greater regioselectivity was the formation of enol acetates at the C-6′ ketone in diacetyl zearalenone. In this case the major product was one derived from enolization in the C-5′ direction to give **29**[26] in 61% isolated yield. The higher melting, less soluble Δ-6′ isomer (**31**) was isolated in ~4% yield.

The identities of the two isomers **29** and **31** were determined by ozonolysis followed by reduction with dimethyl sulfide[27] to the aldehydes **30** and **32**, respectively (Scheme VI). These degradation products were then examined by nmr and mass spectrometry and in the case of **30a** by conversion to **30c**. As expected, the mass spectra of **30a**, **30b**, and **32** exhibit strong peaks at *m/e* 143, 139, and 85, respectively. These peaks are base peaks and result from cleavage of the respective C–O ester bonds.

The conditions under which the enol acetates **29**

(26) Examination of various types of molecular models indicates that the C-5′–C-6′ double bond involves less steric interactions if it is trans.

(27) J. J. Pappas, W. D. Keaveney, E. Gancher, and M. Berger, *Tetrahedron Lett.*, 4273 (1966).

and **31** are formed are not ones which are known[28] to lead cleanly to kinetic products because of the prolonged reaction times necessary for complete conversion of the starting material. Preparation of **29** and **31** using conditions involving the use of *p*-toluenesulfonic acid and acetic anhydride over an extended period of time which gives thermodynamically favored products[28] were preparatively unsuccessful because of slow conversion and a large number of products as determined by tlc. In this case and in the preparation of **21** the fact that conditions known to give thermodynamic product were not successful in producing the desired product suggests kinetic control.

Experimental Section[29]

6-(6-Ethylenedioxy-10-hydroxy-*trans*-1-undecenyl)-β-resorcylic Acid μ-Lactone (2).—Zearalenone[1] (**1**, 10.0 g, 31.6 mmol) was stirred and refluxed for 26 hr with 220 ml of benzene, 30 ml of ethylene glycol, and 0.25 g of *p*-toluenesulfonic acid monohydrate using a water separator. After cooling the mixture, 200 ml of ether and 400 ml of saturated brine were added. The organic layer was separated, washed four times with saturated brine, dried, and concentrated to 11.5 g of white foam. An analytical sample was obtained as a glass by sublimation at 100° (50 μ): uv max 236 mμ (ε 26,300), 274 (11,600), 313 (5760); ir 6.10, 6.22, 6.33 μ; nmr τ 2.14 (s, 1, OH), 2.4 (s, 1, OH), 2.92 (d, 1, *J* = 16 Hz, =CH), 2.15 (m, 2, ArH), 4.18 (d, 1, *J* = 16 cps, =CH), 5.0 (m, 1, CO_2CH), 6.06 (s, 4, OCH_2), and 8.63 (d, 3, *J* = 6 Hz, CH_3).

Anal. Calcd for $C_{20}H_{26}O_6$: C, 66.20; H, 7.23. Found: C, 66.31; H, 7.35.

2-(10-Hydroxy-6-oxo-*trans*-undecenyl)-4,6-dibenzyloxybenzoic Acid μ-Lactone (4).[30]—A mixture of 50 g of **1**, 81 g of benzyl chloride, and 98 g of potassium carbonate was stirred and refluxed for 5 days in 1 l. of acetone. After cooling, the mixture was filtered and the filtrate was concentrated to an oil which was triturated with 1 l. of *n*-hexane to give 70 g of product: mp 130–132°; nmr τ 2.61 (s, 5, C_6H_5), 2.64 (s, 5, C_6H_5), 3.29 (d, 1, *J* = 2 Hz, ArH), 3.50 (d, 1, *J* = 2 Hz, ArH), 3.55 (d, 1, *J* = 16 Hz, =CH), 3.7–4.4 (m, 1, =CH), 4.5–5.1 (m, 1, CO_2CH), 4.96 (s, 2, OCH_2Ph), 4.98 (s, 2, OCH_2Ph), and 8.76 (d, 2, *J* = 6 Hz, CH_3).

Anal. Calcd for $C_{32}H_{34}O_5$: C, 77.08; H, 6.87. Found: C, 76.91; H, 6.62.

2-(10-Hydroxy-6-oxo-*trans*-undecenyl)-4,6-bismethoxymethoxybenzoic Acid μ-Lactone (5).—A 3.18-g (10.0 mmol) portion of zearalenone was dissolved in 75 ml of dimethylformamide (dried with 3A molecular sieves). The stirred solution was cooled with an ice bath and 0.89 g (20.3 mmol) of 54.7% sodium hydride in mineral oil was added. After stirring for 30 min at 0°, 1.7 g (21 mmol) of chloromethylmethyl ether in 25 ml of dimethylformamide was added dropwise with stirring over a period of 20 min. Stirring was continued for 30 min at 0° and about 50% of the solvent was removed *in vacuo*. The remainder was then poured onto 150 g of ice. The resulting precipitate was collected, washed well with water, and dissolved in methylene chloride. The methylene chloride solution was dried and concentrated to 4.3 g of solid, which was recrystallized from methylene chloride–*n*-hexane to give 2.96 g (73%) of light yellow crystalline chunks: mp 140.5–143.0°; uv max 222.5 mμ (ε 26,800), 254 (12,700), 296 (1880); ir (Nujol mull) 5.84, 5.91 μ; nmr τ 3.15 (d, 1, *J* = 2.5 Hz, ArH), 3.28 (d, 1, *J* = 2.5 Hz, ArH), 3.57 (d, 1, *J* = 16 Hz, =CH), 3.86 (m, 1, =CH), 4.83 (s, 4, OCH_2O), 6.52 (s, 6, OCH_3), and 8.67 (d, 3, *J* = 6 Hz, CH_3).

Anal. Calcd for $C_{22}O_{30}O_7$: C, 65.01; H, 7.44. Found: C, 65.11; H, 7.48.

2-(6-Ethylenedioxy-10-hydroxy-*trans*-1-undecenyl)-4,6-methoxymethoxybenzoic Acid μ-Lactone (6).—Using 29 g of crude **2**, crude **6** was prepared in essentially the same manner as **5**. Chromatography on 600 g of Fluorisil using benzene–ethyl acetate as an eluent yielded crystalline material in early fractions. The entire eluent was then concentrated to a gum and recrystallized from methanol at −5° (using a seed crystal) to give 30 g of product: mp 70–72°; uv max 221 mμ (ε 31,500), 255 (13,200), 295 (31,500), 255 (13,200), 295 (ε 1710); ir 5.83 μ; nmr τ 3.18 (d, 1, *J* = 2.5 Hz, ArH), 3.33 (d, 1, *J* = 2.5 Hz, ArH), 3.6–3.8 (m, 2, =CH), 4.86 (s, 4, OCH_2O), 6.12 (s, 4, OCH_2), 6.55 (s, 6, OCH_3), and 8.65 (d, 3, *J* = 6 Hz, CH_3).

Anal. Calcd for $C_{24}H_{34}O_8$: C, 63.98; H, 7.61. Found: C, 64.07; H, 7.58.

2-(6,10-Dihydroxy-*trans*-undecenyl)-4,6-bismethoxymethoxybenzoic Acid μ-Lactone (7).—A solution of 4.65 g of **5** in 50 ml of methanol was cooled in an ice bath and 1.0 g of $NaBH_4$ was added portionwise over a period of 5 min. After stirring for 15 min at 0° and 0.5 hr at room temperature the mixture was taken up in 400 ml of saturated brine which contained excess hydrochloric acid. The mixture was extracted with ether and the ether extracts were washed with saturated brine, dried, and concentrated to 4.5 g of a solid of low crystallinity.

Anal. Calcd for $C_{22}H_{32}O_7$: C, 64.68; H, 7.90. Found: C, 64.73; H, 7.91.

2-(6-Acetoxy-10-hydroxy-*trans*-undecenyl)-4,6-bismethoxymethoxybenzoic Acid μ-Lactone (8).—A 4.3-g portion of **7** was treated with 20 ml of pyridine and 15 ml of acetic anhydride for 18 hr before pouring into ice. The mixture was extracted with ether, which was washed with dilute HCl and saturated brine before *in vacuo* concentration to 4.6 g of semisolid.

Anal. Calcd for $C_{24}H_{34}O_8$: C, 63.98; H, 7.61. Found: C, 63.82; H, 7.54.

5,7-Dibenzyloxy-1,3-dihydro-1-oxo-3-(10-methyl-1,11-dioxaspiro[5.5]undecan-2-yl)benzo[*c*]furan (10).—A 5.73-g (1.15 mmol) portion of **4** was treated with 3.00 g (1.18 mmol) of osmium tetroxide and worked up essentially according to the procedure of Corey, *et al.*,[31] to give 6.3 g of gummy residue **9** which was much more polar on tlc than starting material. A 0.83-g portion of this residue was dissolved in 10 ml of chloroform, and 2 drops of concentrated hydrochloric acid were added. After standing for 15 hr at room temperature, the mixture was concentrated *in vacuo* to a foam which was dissolved in ether. The ether solution was decanted from an insoluble yellow oil, filtered, concentrated to 15 ml of hot ether, and precipitate. After cooling, 0.41 g of colorless needles were collected: mp 152–156°; ir 5.72 μ; nmr τ 2.63 (s, 10, C_6H_5), 3.3–3.45, (m, 2, ArH), ~4.7 (m, 1, OCHAr), 4.78 (s, 2, $PhCH_2O$), 4.92 (s, 2, $PhCH_2O$), 4.92 (s, 2, $PhCH_2O$), ~5.4 (m, 1, OCH), and ~6.2 (m, 1, OCH).

Anal. Calcd for $C_{32}H_{34}O_6$: C, 74.68; H, 6.06. Found: C, 74.42; H, 6.55.

1,3-Dihydro-5,7-dihydroxy-1-oxo-3-(10-methyl-1,11-dioxaspiro[5.5]undecan-2-yl)benzo[*c*]furan (11).—A 4.15-g (8.1 mmol) portion of **10** was hydrogenated in 200 ml of ethyl acetate in the presence of 0.5 g of 10% palladium on carbon catalyst. The reaction was carried out in a Parr bomb at 35-lb pressure. Uptake stopped at theory after 2.5 hr. The catalyst was removed by filtration, and the filtrate was concentrated to a solid which was triturated with *n*-hexane and collected on a filter to give 2.45 g (89%) of wide-melting solid: ir 5.8 μ; nmr (DMSO) τ −1 to 0 (very broad, 2, OH), 3.66 (s, 2, ArH), 4.78 (d, 1, *J* = 4 Hz, OCHAr), 5.7 (d of d, 1, *J* = 4 and 9 Hz, OCH), and 6.35 (m, 1, OCH).

Anal. Calcd for $C_{15}H_{22}O_6$: C, 64.65; H, 6.63. Found: C, 64.85; H, 6.69.

2-(6-Ethylenedioxy-10-hydroxy-1-oxoundecanyl)-4,6-bismethoxymethoxybenzoic Acid μ-Lactone (12).—A 4.5-g (10.0 mmol) portion of **6** was dissolved in 150 ml of tetrahydrofuran

(28) H. O. House and B. M. Trost, *J. Org. Chem.*, **30**, 2502 (1965).

(29) Unless stated otherwise, drying of solutions was with anhydrous magnesium sulfate, and concentration was by removal of the solvent at reduced pressure using a rotary evaporator. Infrared spectra were determined on Perkin-Elmer 137 and 237B recording spectrophotometers in chloroform solution. Nuclear magnetic resonance spectra were determined in deuteriochloroform on a Varian Associates A60 recording spectrometer using tetramethylsilane as an internal standard. Ultraviolet spectra were determined in methanol using a Cary 14 recording spectrophotometer. Mass spectra were run at 70 eV using an LKB 9000 mass spectrograph. Thin layer chromatograms were run on Analtech, Inc., silica gel G plates utilizing iodine or ceric sulfate development. Melting points were run on a Koffler block and are uncorrected. Analyses were performed by R. Boos and associates of these laboratories.

(30) Procedure of Dr. R. Czaza of these laboratories. This compound was first prepared and characterized by workers at Commercial Solvents Co. (see ref 1b for these workers).

(31) E. J. Corey, M. Ohno, R. B. Mitra, and P. A. Vatakencherry, *J. Amer. Chem. Soc.*, **86**, 478 (1964).

(distilled from lithium aluminum hydride and stored over 3A molecular sieves). The mixture was stirred under a nitrogen atmosphere and cooled to 0° before 20 ml of 0.5 *M* diborane in tetrahydrofuran was added dropwise over a period of 5 min. The temperature was kept below 1° during addition. After stirring for 1 hr at 0° the cooling bath was removed and stirring was continued for 23 min as the temperature rose to 18°. At this time the reaction mixture was cooled to −12° and 10 ml of water was added dropwise over a period of 11 min while the temperature was maintained below −10°. Stirring and cooling was continued as 25 ml of 2.5 *N* sodium hydroxide was added dropwise over a period of 3 min (temperature <−4°) followed by dropwise addition of 25 ml of 30% hydrogen peroxide over a period of 2 min (temperature <−2°). The cooling bath was then removed and the mixture was stirred for 30 min before being extracted with 400, 200, and 100 ml of ether. The combined ether extracts were washed with saturated brine, dried, and concentrated to 4.9 g of colorless oil. This residue was stirred for 14 hr with pyridine–chromium trioxide complex formed from 5.0 g of chromium trioxide and 50 ml of pyridine. After dilution with 50 ml of ether the insoluble salts were removed by filtration and washed ten times with 300-ml portions of saturated brine, dried, and concentrated to 4.66 g of viscous yellow oil. A 10.6-g portion of this residue (from runs of 5.0 and 6.0 g) was chromatographed on a 4.4-cm dry column of 350 g of silica gel using 30% ethyl acetate in benzene as an eluent. Fractions containing product (3.9 g) were then rechromatographed on an identical column. In this manner, 3.5 g of product was isolated. Also found in the crude reaction product were about 20% of starting material **6**, 4% of compound **15**, and about 20% of material **14** whose ir showed a 5.71-μ (phthalide) carbonyl. An analytical sample of the product was obtained as a glass by sublimation: uv max 217 mμ (ε 25,500), 253 (6350), 312 (2720); ir 5.82, 5.95 μ; nmr τ 2.90 (d, 1, *J* = 2.5 Hz, ArH), 2.98 (d, 1, *J* = 2.5 Hz, ArH), 4.80 (s, 4, OCH_2O), 6.12 (s, 4, OCH_2), 6.51 (s, 6, OCH_3), and 7.05 (m, 2, $ArCOCH_2$).

Anal. Calcd for $C_{24}H_{34}O_9$: C, 61.79; H, 7.35. Found: C, 61.90; H, 7.30.

6-(1,6-Dioxo-10-hydroxyundecanyl)-β-resorcylic Acid μ-Lactone (13).—A 2.1-g portion of **12** was refluxed and stirred under a nitrogen atmosphere for 4 hr with 240 mg of *p*-toluenesulfonic acid monohydrate, 35 ml of benzene, 6.5 ml of ethylene glycol, and 1 ml of water. After being cooled the mixture was taken up in 200 ml of ether. The ether solution was washed five times with saturated brine, dried, and concentrated to 1.4 g of foam which was chromatographed on 170 g of activity 3 neutral alumina on a 2.5-cm column. Elution with 2% methanol in ethyl acetate gave an impurity and elution with 10% methanol plus 1% acetic acid in ethyl acetate yielded 1.1 g (73%, mp 167–171°) of product. An analytical sample was obtained by washing with ether: mp 172.5–174.5°; ir 5.85, 6.03, 6.19 μ; nmr τ −0.93 (s, 1, OH), ~2 (very broad, 1, OH), 3.57 (d, 1, *J* = 2.5 Hz, ArH), and 3.85 (d, 1, *J* = 2.5 Hz, ArH).

Anal. Calcd for $C_{18}H_{22}O_6$: C, 64.65; H, 6.63. Found: C, 64.68; H, 6.73.

2-(6-Ethylenedioxy-10-hydroxy-3-oxo-*trans*-1-undecenyl)-4,6-bismethoxymethoxybenzoic Acid μ-Lactone (15).—A 4.00-g (8.9 mmol) portion of **6** was stirred for 47 hr at 27–28° with chromium trioxide–pyridine complex formed from 8.0 g of chromium trioxide and 100 ml of pyridine. The mixture was then added to 600 ml of ether and the insoluble precipitate was removed by filtration and washed well with ether. The combined filtrate and washings were then washed five times with 800-ml portions of saturated brine, dried with sodium sulfate, and concentrated to 4.0 g of viscous yellow oil which was 85% one spot on tlc (30% methyl ethyl ketone–70% *n*-hexane as an eluent). This residue was chromatographed on a 4.4-cm dry column of 300 g of silica gel using 35% ethyl acetate in benzene as an eluent. In this manner 2.4 g (59%) of pure material was separated. An analytical sample was obtained as a colorless glass by sublimation: uv max 231 mμ (ε 18,100), 291 (17,850); ir 5.83, 6.03, 6.11, 6.24 μ; nmr τ 2.56 (d, 1, *J* = 16 Hz, =CH), 2.96 (d, 1, *J* = 2.5 Hz, ArH), 3.14 (d, 1, *J* = 2.5 Hz, ArH), 3.46 (d, 1, *J* = 16 Hz, =CHCO), 4.83 (s, 4, OCH_2O), 5.86 (m, 1, CO_2CH), 6.10 (s, 4, OCH_2), 6.54 (s, 6, OCH_3), and 8.63 (d, 3, *J* = 6.5 Hz, CH_3).

Anal. Calcd for $C_{24}H_{32}O_9$: C, 62.05; H, 6.94. Found: C, 62.03; H, 6.94.

6-(3,6-Dioxo-10-hydroxy-*trans*-1-undecenyl)-β-resorcylic Acid μ-Lactone (16).—A 1.9-g portion of **15** was refluxed for 6 hr under nitrogen with 35 ml of benzene, 8 ml of ethylene glycol, 260 mg of *p*-toluenesulfonic acid monohydrate, and 1 ml of water. After cooling the mixture was taken up in 100 ml of ether and 100 ml of saturated brine. The ether layer was separated, washed four times with saturated brine, dried, and concentrated to 1.3 g of yellow foam. To this residue, under nitrogen, was added 20 ml of acetone, 20 ml of ethanol, 2 ml of water, and 0.3 g of *p*-toluenesulfonic acid monohydrate. The mixture was stirred and refluxed for 3 hr and concentrated *in vacuo*. The residue was triturated with water and the insoluble precipitate was collected on a filter and washed ten times with 10-ml portions of water to give 0.98 of crude product. Two recrystallizations from nitromethane gave 0.98 g of crude product. Two recrystallizations from nitromethane gave 0.48 g of analytical sample: mp 214.5–216.0°; uv max 216 mμ (ε 20,750), 247.5 (26,200), 286 (9030), 300 (8420); ir (Nujol mull) 5.92, 6.04, 6.2 μ; nmr τ −0.75 (broad, 2, OH), 2.23 (d, 1, *J* = 16 Hz, =CH), 3.53 (d, 1, *J* = 16 Hz, =CH), 3.57 (s, 2, ArH), and 8.73 (d, 3, *J* = 6 Hz, CH_3).

Anal. Calcd for $C_{18}H_{20}O_6$: C, 65.05; H, 6.07. Found: C, 64.80; H, 6.33.

2-(3,6-Dioxa-10-hydroxy-*trans*-1-undecenyl)-4,6-bismethoxymethoxybenzoic Acid μ-Lactone (17).—A 1.0-g portion of **5** was stirred for 11 days at 25–30° with chromium trioxide–pyridine complex formed from 2.0 g of chromium trioxide and 30 ml of pyridine. The mixture was worked up as described in the preparation of **15** to give 0.69 g of yellow solid whose tlc (20% ethyl acetate on benzene as an eluent) showed it to be 50% starting material (after only 2 days reaction, about 85% starting material was still unreacted), 10% unknown material, and 40% product. The product was isolated by preparative tlc and recrystallized from methanol to give an analtycal sample: mp 117–119.5°; uv max 227.5 mμ (ε 17,600), 290 (12,600); ir 5.84, 6.01, 6.14, 6.25 μ; nmr τ 2.56 (d, 1, *J* = 16 Hz, ArCH=), 3.03 (d, 1, *J* = 2.5 Hz, ArH), 3.13 (d, 1, *J* = 2.5 Hz, ArH), 3.47 (d, 1, *J* = 16 Hz, =CHCO), 4.82 (s, 2, OCH_2), 6.53 (s, 6, OCH_3), and 8.65 (d, 3, *J* = 6.5 Hz, CH_3).

Anal. Calcd for $C_{22}H_{28}O_8$: C, 62.84; H, 6.71. Found: C, 62.55; H, 6.89.

2-(6-Acetoxy-10-hydroxy-3-oxo-*trans*-1-undecenyl-4,6-bismethoxymethoxybenzoic Acid μ-Lactone (18).—A 387-mg portion of **8** was treated as in the preparation of **15** to give 0.35 g of crude product which was ~60% one spot on tlc (30% ethyl acetate–benzene). Purification of preparative tlc gave 0.18 g of one-spot material which was purified for analysis by sublimation at 190° (50 μ): uv max 227 mμ (ε 15,400); ir 5.84, 6.02, 6.13, 6.23 μ; nmr τ 2.56 (d, 1, *J* = 15.5 Hz, ArCH=), 2.95 (d, 1, *J* = 2 Hz, ArH), 3.12 (d, 1, *J* = 2 Hz, ArH), 3.46 (d, 1, *J* = 15.5 Hz, =CHCO), 4.82 (s, 4, OCH_2O), and 6.54 (s, 6, OCH_3).

Anal. Calcd for $C_{24}H_{32}O_9$: C, 62.05; H, 6.94. Found: C, 61.84; H, 6.87.

2-(3′,10′-Dihydroxy-6′-ethylenedioxy-*trans*-1′-undecenyl)-4,6-bismethoxymethoxybenzoic Acid μ-Lactone (19).—A 1.85-g sample of **15** was dissolved in 25 ml of methanol and the solution was stirred as 0.33 g of sodium borohydride was added. The mixture was stirred for 30 min, 200 ml of chloroform was added, and the mixture was washed with dilute hydrochloric acid and saturated brine. The chloroform solution was then dried and concentrated to 1.83 g of colorless gum. An analytical sample was obtained as a glass by sublimation: uv max 221 mμ (ε 30,700), 252.5 (12,500), 295 (1970); ir 5.83 μ.

Anal. Calcd for $C_{24}H_{34}O_9$: C, 61.79; H, 7.35. Found: C, 62.05; H, 7.33.

6-[10-Hydroxy-6-(2-hydroxylethoxy)-3,6-oxy-*trans*-1-undecenyl]-β-resorcylic Acid μ-Lactone (20).—To 513 mg of **19** was added 5 ml of acetone, 5 ml of ethanol, 0.5 ml of water, and 100 mg of *p*-toluenesulfonic acid monohydrate. The mixture was stirred and refluxed under nitrogen for 6 hr and the solvent was removed *in vacuo*. The residue was taken up in ether and the ether solution was washed with saturated brine, dried, and concentrated to 0.45 g of foam. To this foam was added 13 ml of benzene, 3 ml of ethylene glycol, 0.5 ml of water, and 100 mg of *p*-toluenesulfonic acid monohydrate. The mixture was stirred and refluxed under nitrogen for 7 hr. Work-up as before gave 375 mg of colorless foam. This material was dissolved in 10 ml of chloroform. On standing at −5°, a precipitate separated and was collected on a filter to give 86 mg, mp 243–248°. An analytical sample was prepared by two recrystallizations from chloroform: mp 245–246°; uv max 235 mμ (ε 28,400), 274 (12,300), 316 (5860; with base added 256 (21,600), 305 (15,200), 315

(15,400); ir (Nujol mull) 5.89, 6.07; 6.24 μ; nmr (DMSO) τ −1.83 (broad, 1, OH), −0.4 (very broad, 1, OH), 2.84 (d, 1, J = 16 Hz, =CH), 3.52 (d, 1, J = 2.5 Hz, ArH), 3.68 (d, 1, J = 2.5 Hz, ArH), 4.41 (d of d, 1, J = 16 and 9 Hz, =CH), 5.1 (m, 1, CO_2CH), 5.4 (m, 1, OH, disappears on spiking with D_2O), 6.2 (m, 1, OCH), 6.5 (m, 4, OCH_2), and 8.64 (d, 3, J = 6 Hz, CH_3); mass spectrum of tristrimethylsilyl derivative m/e 594.

Anal. Calcd for $C_{20}H_{26}O_7$: C, 63.48; H, 6.93. Found: C, 63.70; H, 7.16.

Acetylation of 20.—A 30-mg sample of **20** was dissolved in 0.6 ml of pyridine, and 0.4 ml of acetic anhydride was added with stirring. After standing for 15 hr the mixture was diluted with 10 ml of ice–water. The water was decanted from the resultant gum, which was washed with water and taken up in ether. The ether solution was dried and concentrated to 35 mg of colorless gum which was examined by nmr: τ 2.87 (d, 1, J = 2 Hz, ArH), 3.15 (d of d, 1, J = 1.5 and 16 Hz, =CH), 3.23 (d, 1, J = 2 Hz, ArH), 4.23 (d of d, 1, J = 16 and 5 Hz, =CH), 4.80 (m, 1, CO_2CH), 5.85 (m, 2, OCH_2), 5.9 (m, 1, OCH), 6.4 (m, 2, OCH_2), 7.73 (s, 3, $COCH_3$), 7.76 (s, 3, $COCH_3$), 7.93 (s, 3, $COCH_3$), and 8.66 (c, 3, J = 6.5 Hz, CH_3).

2-{7-[(Cyclohexyloxy)methylene]-10-methyl-6-oxo-1-undecenyl}-4,6-dibenzyloxybenzoic Acid μ-Lactone (22).—A 19-g portion of **4**, 4.2 g of 54.7% sodium hydride in mineral oil, and 300 ml of benzene (dried with 3A molecular sieves) were stirred under a nitrogen atmosphere for 5 min, and 1 ml of *tert*-butyl alcohol (dried with 3A molecular sieves) was added. After stirring for 15 min at room temperature, the mixture was refluxed for 15 min and cooled to room temperature, and 9.6 ml (8.4 g) of ethyl formate (dried with 3A molecular sieves) was added. The mixture was then stirred for 18 hr and 2 ml of additional ethyl formate was added. After stirring for 3 hr more the mixture was added to 1 l. of water and 500 ml of ether. The water layer was separated and made acidic with sodium dihydrogen phosphate before extraction with ether. The ether extract was dried and concentrated to 20 g of pink gum whose tlc (30% acetone–70% *n*-hexane) showed an 8:1 mixture of **21** and its C-5′ isomer. Pure **21** was obtained by preparative tlc: ir 5.72, 5.82, and 6.25 μ; nmr τ −5.16 (d, 1, J = 5.5 Hz, C=COH), 1.70 (d, 1, J = 5.5 Hz, C=CHOH), 2.65 (s, 5, ArH), 2.68 (s, 5, ArH), 3.35 (d, 1, J = 2.5 Hz, ArH), 3.44 (d, 1, J = 16 Hz, C=CH), 3.49 (d, 1, J = 2.5 Hz, ArH), 3.8–4.1 (m, 1, C=CH), 4.5–4.9 (m, 1, CO_2CH), 4.95 (s, 4, $ArCH_2$), and 8.75 (d, 3, J = 6.5 Hz, CH_3).

A mixture of 14.5 g of the crude **21** and its C-5′ isomer and 400 ml of benzene was boiled as 50 ml of distillate was removed by a Dean–Stark water separator. The mixture was cooled, and 50 mg of *p*-toluenesulfonic acid monohydrate and 3.6 ml of cyclohexanol was added. The mixture was then refluxed for 15 hr with the use of a Dean–Stark water separator. The Dean–Stark trap was then drained and filled with 3A molecular sieves and refluxing was continued for 45 hr. After cooling and addition of 400 ml of ether, the mixture was washed with dilute sodium hydroxide followed by saturated brine. After being dried the organic layer was concentrated to 13 g of orange gum whose tlc (10% ethyl acetate–90% benzene) exhibited two spots in a ~8:1 ratio. This residue was chromatographed on a 6.6-cm dry column of 390 g of silica gel H using 10% ethyl acetate–90% benzene as an eluent. In this manner, 6.8 g of **22**, which was free of C-5′ isomer, was isolated as a glass. An analytical sample was obtained by grinding a sample to a powder and drying at 50 μ: uv max 227 mμ (ϵ 36,000) and 258 (26,700); ir 5.83, 6.01, 6.16, 6.26, and 6.34 μ.

Anal. Calcd for $C_{39}H_{44}O_6$: C, 76.94; H, 7.29. Found: C, 76.87; H, 7.34.

2-(7-Formyl-10-hydroxy-*trans*-1,6-undecadienyl)-4,6-dibenzyloxybenzoic Acid μ-Lactone (23).—To a stirred solution of 5.7 g (9.4 mmol) of **22** in 110 ml of methanol was added, in small portions over a period of 10 min, 2.5 g of sodium borohydride. The mixture was then stirred for 75 min and concentrated *in vacuo* to a solid residue which was taken up in 200 ml each of ether and saturated brine. The layers were separated and the aqueous layer was extracted once with ether. The combined ether layers were then washed with saturated brine, dried, and concentrated *in vacuo* to 5.45 g of colorless gum. This gum was stirred under nitrogen for 4 hr in a mixture of 100 ml of ether and 100 ml of 3 *N* hydrochloric acid. An additional 200 ml of ether was then added and the organic layer was separated, washed with saturated brine, and dried before concentration *in vacuo* to 5.0 g of slightly colored gum. This residue was shown by tlc (10% ethyl acetate–90% benzene) to be ~75% product. Purification of a 4.5-g portion of this residue was achieved by chromatography on 200 g of silica gel H in a 4.5-cm dry column (10% ethyl acetate–90% benzene). This procedure gave 3.16 g (73%) of a colorless gum which was one spot on tlc. An analytical sample was obtained as a glass by sublimation at 170° (50 μ): uv max 222 mμ (ϵ 47,800), 264 (7800), and 290 (2780); ir 3.67, 5.82, 5.95, 6.06, and 6.10 μ; nmr τ 0.64 (s, 1, CHO), 2.66 (s, 5, C_6H_5), 2.69 (s, 5, C_6H_5), 3.33 (d, 1, J = 2.5 Hz, ArH), 3.51 (d, 1, J = 2.5 Hz, ArH), 4.98 (s, 4, OCH_2Ph), and 8.77 (d, 3, J = 6 Hz, CH_3).

Anal. Calcd for $C_{33}H_{34}O_5$: C, 77.62; H, 6.71. Found: C, 77.36; H, 6.57.

6-(7-Formyl-10-hydroxyundecyl)-β-resorcylic Acid μ-Lactone (24).—A 2.20-g portion of **23** was hydrogenated at atmospheric pressure in 50 ml of ethyl acetate in the presence of 1.1 g of 10% palladium on carbon (no prehydrogenation of the catalyst). Hydrogenation was stopped after 3 hr and 413 ml uptake. The catalyst was removed by filtration. Concentration of the filtrate *in vacuo* gave 1.31 g of slightly colored tacky gum which was 70% one spot (R_f 0.3) on tlc (10% ethyl acetate–90% benzene). This material was purified by chromatography on 60 g of silica gel H in a dry 3.5-cm column (10% ethyl acetate–90% benzene). Early fractions yielded material with one benzyl group remaining, [ir 3.67, 5.75, 6.03, and 6.14 μ; nmr τ 2.65 (s, 5, C_6H_5) and 4.97 (s, 2, CH_2Ar)], while later fractions gave material with a reduced formyl group [ir 2.79, 3.08, 6.10, and 6.17 μ; nmr τ 6.5 (m, 2, CH_2OH)]. The intermediate fractions yielded 0.72 g (50%) of pure product which was epimeric at C-7: mp 40–140°; uv max 219.5 mμ (ϵ 21,900), 265 (13,100), and 303 (ϵ 5280); ir 2.74, 2.81, 3.0, 3.70, 5.82, 6.10, and 6.18 μ; nmr τ −2.23 (s, 0.6, OH), −2.17 (s, 0.4, OH), 0.30 (s, 0.4, CHO), and 0.35 (s, 0.6, CHO).

Anal. Calcd for $C_{19}H_{26}O_5$: C, 68.24; H, 7.84. Found: C, 68.17; H, 7.89.

Isolation of Epimers of 24.—The crude hydrogenation product from three runs as described in the preparation of epimeric **24** (10.3 g) was recrystallized twice from benzene to give 1.2 g of crude isomer b which was not pure by tlc, mp 152–155°. This sample was chromatographed on 120 g of Baker silica gel packed in benzene and gave 1.09 g of material that was one spot on tlc (R_f 0.4, 10% ethyl acetate–90% benzene). This material was recrystallized from benzene to give 820 mg of pure isomer **24b**: mp 148–152°; nmr τ −2.5 (s, 1, OH), and 0.30 (s, 1, CHO).

Anal. Calcd for $C_{19}H_{26}O_5$: C, 68.24; H, 7.81. Found: C, 68.42; H, 7.77.

To the filtrate of the first recrystallization of the 10.3 g of crude **24** mentioned above, *n*-hexane was added and 1.0 g of precipitate separated and was collected on a filter. Recrystallization from benzene gave 600 mg of crude isomer **24a** which was impure by tlc. Chromatography in 60 g of silica gel as described in the purification of isomer **24b** gave 0.40 g of pure isomer **24a**: mp 141–146°; nmr τ −2.13 (s, 1, OH), and 0.35 (s, 1, CHO).

Anal. Calcd for $C_{19}H_{26}O_5$: C, 68.24; H, 7.84. Found: C, 68.54; H, 7.82.

6-(10-Hydroxy-7-oxoundecyl)-β-resorcylic Acid μ-Lactone (25).—The epimeric mixture **24** (445 mg) was dissolved in 5 ml of pyridine (dried with 3A molecular sieves) and 7 ml of acetic anhydride. After standing for 15 hr the mixture was poured onto ice. The resultant gum was extracted with ether and the ether extracts were washed with saturated brine, dried, and concentrated *in vacuo* to 475 mg of slightly colored gum. This residue was added to 100 mg of *p*-toluenesulfonic acid monohydrate and 20 ml of freshly distilled isopropenyl acetate. The mixture was slowly distilled for 10 hr (5 ml of distillate collected), refluxed for 13 hr, and distilled for another hour (5 ml of distillate collected). The remainder of the isopropenyl acetate was removed *in vacuo*, and the residue was taken up in ether. The ether solution was washed with saturated brine, dried, treated with activated charcoal, and concentrated to 554 mg (90%) of yellow gum, which was one spot on tlc (R_f 0.25, 10% ethyl acetate–90% benzene). An analytical sample of the enol acetate of **24** diacetate was prepared by purification by preparative tlc followed by sublimation at 150° (50 μ) to give a colorless glass: ir 5.6–5.7 μ; nmr τ 3.13 (s, 1, =CH), 3.17 (d, 1, J = 2.5 Hz,

ArH), 3.26 (d, 1, J = 2.5 Hz, ArH), 7.82 (s, 3, $COCH_3$), 7.83 (s, 3, $COCH_3$), and 7.95 (s, 3, $COCH_3$).

Anal. Calcd for $C_{25}H_{32}O_8$: C, 65.20; H, 7.00. Found: C, 65.44; H, 7.13.

A 400-mg sample of the crude enol acetate was ozonized in methanol and treated with dimethyl sulfide as described in the ozonolysis of **10**. Concentrations *in vacuo* gave 489 mg of brown oil. To this residue was added 8 ml of methanol, 8 ml of dioxane, and 3 ml of 2.5 *N* sodium hydroxide. After standing for 2 hr the solvent was removed *in vacuo* and the residue was dissolved in 50 ml of water. The aqueous solution was washed with ether, acidified with concentrated hydrochloric acid, and extracted with ether. The ether extract was washed with saturated brine, dried, and concentrated *in vacuo* to 278 mg of pink gum whose tlc (20% ethyl acetate–80% benzene) showed it to be ~85% one spot at R_f 0.4. This material was purified by preparative tlc (4% methanol–96% chloroform) to give 155 mg (56%) of crystalline product, mp 167–170°. An analytical sample was obtained by partial recrystallization from benzene: mp 168–170.5°; ir 5.86, 6.10, and 6.17 μ; nmr τ −1.65 (s, 1, OH), 0.93 (s, 1, OH), 3.68 (d, 1, J = 3 Hz, ArH), 3.75 (d, 1, J = 3 Hz, ArH), 4.82 (q, 1, J = 6 Hz, COCH), and 8.63 (d, 3, J = 6 Hz, CH_3); mass spectrum m/e (rel intensity) 320 (11), 302 (5), 265 (51), 177 (15), 163 (48), 150 (23), 124 (39), 123 (33), 111 (100), 98 (35), 69 (32), 55 (67), 41 (34).

Hydroxymethylation of Dimethoxyzearalanone and Degradation of the Main Isomer to Diacid 28.—In 21 ml of dry benzene, 1044 mg of dimethoxyzearalanone[1b] was dissolved and 330 mg of sodium hydride (51% dispersion in mineral oil) was added, followed by 0.15 ml of *tert*-butyl alcohol. The mixture was heated for 3 min to 60° and allowed to stir for 15 min at room temperature. After addition of 0.75 ml of freshly distilled ethyl formate, it was stirred overnight and became dark brown. Work-up consisted of quenching by pouring onto 25 g of ice and adddition of 2 ml of 2.5 *N* sodium hydroxide followed by two extractions with ether. The aqueous portion was acidified with sodium dihydrogen phosphate and extracted three times with ether. Upon drying and concentrating, the residue was only 1020 mg.

A total of 1000 mg was chromatographed on ten silica gel plates (8 × 8 × 1000 μ) and developed with 20% acetone in hexane, giving good separation into two bands. The less polar fraction (R_f 0.3) was homogeneous but still oily and weighed 460 mg (**26**).

The homogeneous, more polar fraction (R_f 0.45) was also oily, 150 mg, and undistinguished by ir, uv, or nmr from either the more abundant isomer or the total crude: uv max 281 mμ (ϵ 5000); with base added 302.5 (15,100), 245 (4980); ir (neat) 5.83, 5.88, 6.25 μ.

Degradation to 28.—A 230-mg portion of **26** was dissolved in 8 ml of ethyl acetate, cooled to −70°, and exposed for a total of 12 min to a stream of ozone. During this period the initially orange-colored solution became light yellow. After purging the mixture with nitrogen at 0°, 6 ml of glacial acetic acid was added at this temperature, followed by 1.5 ml of 30% hydrogen peroxide solution. The mixture was allowed to warm to room temperature and stirred for 3 hr. It was worked up after the addition of 30 ml of water containing 4 g of sodium bisulfite and final acidification to pH 2. The combined ethyl acetate extracts were dried and concentrated to dryness, yielding 180 mg of amorphous solid (**27**).

(A 70-mg sample of this solid was purified by chromatography on silica gel plates using a 50:50 mixture of acetone–hexane as an eluent. The major band yielded 40 mg of noncrystalline material which had a molecular ion at m/e 396, corresponding to **27**.)

A 100-mg sample of crude **27** was hydrolyzed by treatment with 5 ml of 2.5 *N* sodium hydroxide on the steam bath for 16 hr.

The ether extracts, after acidification, yielded 80 mg of viscous oil.

On preparative tlc the latter separated into two bands; the major product was crystallized from ether, yielding 40 mg of material, mp 110–111°. Its mass spectrum was very similar to that of **27** if the latter's molecular ion is disregarded. It was assigned to diacid structure **28**, and its identity was confirmed by melting point, mixture melting point, and ir and tlc with an authentic specimen[1b] kindly supplied by Dr. Hodge from CSC.

2-(6-Acetoxy-10-hydroxy-*trans*-1,5-undecadienyl)diacetoxybenzoic Acid μ-Lactone (29).—A 12.5-g (30 mmol) portion of zearalenone diacetate,[1b] 200 g of *p*-toluenesulfonic acid monohydrate, and 200 ml of isopropenyl acetate were stirred and warmed with gradual distillation through a 2.5 × 25 cm Vigreux column for 45 hr. During this time 50 ml of distillate was collected at a stillhead temperature of about 60°. The distillate temperature was then raised to 95° and 50 ml of distillate was collected. The cooled residue was then taken up in a mixture of 400 ml of ether, 350 ml of saturated brine, and 50 ml of 2.5 *N* NaOH. The ether layer was separated, washed four times with saturated brine, dried with sodium sulfate, and concentrated to 18 g of viscous brown oil which was dissolved in 75 ml of methanol and cooled to −5°. The precipitate was collected to give 8.46 g (61%) of slightly colored crystals, mp 120–123°. Recrystallization from methanol gave an analytical sample: mp 124–125°; uv max 219.5 mμ (ϵ 24,800), 252 (14,300); ir 5.66, 5.75, 5.84 μ; nmr τ 2.89 (d, 1, J = 2 Hz, ArH), 3.16 (d, 1, J = 2 Hz, ArH), 3.48 (d, 1, J = 15 Hz, =CH), 3.8–4.3 (m, 1, =CH), 4.5–5.1 (m, 2, OCH), 7.74 (s, 3, $COCH_3$), 7.77 (s, 3, $COCH_3$), 7.88 (s, 3, $COCH_3$), and 8.81 (d, 3, J = 7 Hz, CH_3); mass spectrum m/e (rel intensity) 112 (1), 125 (100), 176 (30), 218 (40), 300 (3), 342 (5), 402 (3), 444 (2).

Anal. Calcd for $C_{24}H_{28}O_8$: C, 64.85; H, 6.35. Found: C, 65.10; H, 6.16.

Ozonolysis of 29.—A 400-mg portion of **29** was added to 65 ml of ethanol. The mixture was stirred, cooled in a Dry Ice–acetone bath, and saturated with ozone. After 10, 20, and 60 min of stirring, the mixture was again saturated with ozone. The cooling bath was then removed, and the mixture was stirred at room temperature for 15 min before flushing with nitrogen. Dimethyl sulfide[27] (1 ml) was added, and the solution was stirred for 65 hr at room temperature (an aliquot taken after 15 hr exhibited an ir with a 5.47 μ carbonyl of moderate strength which was not present after 65 hr). The mixture was then concentrated to an oil whose tlc (30% ethyl acetate in benzene) indicated a small amount of starting material (R_f 0.50), a major spot at R_f 0.45, and a large amount of very polar material. This residue was dissolved in ether and extracted with saturated sodium bicarbonate. The ether layer was dried and concentrated to 147 mg of residue which contained (tlc) ~90% of the material at R_f 0.45 and starting material. A 37-mg sample of oil containing only material of R_f 0.45 and a more polar spot was separated by preparative tlc and treated with 20 ml of pyridine and 400 ml of acetic anhydride. This gave 37 mg of colorless oil that was one spot at R_f 0.45 and is assigned structure **30a**: ir 3.67, 5.64, and 5.80 μ; nmr τ −0.06 (s, 1, CHO), 2.42 (d, 1, J = 2.5 Hz, ArH), 2.71 (d, 1, J = 2.5 Hz, ArH), 4.8 (m, 1, CO_2CH), 5.86 (q, 2, J = 7 Hz, CO_2CH_2), 7.80 (s, 3, $COCH_3$), 7.82 (s, 3 $COCH_3$), 8.62 (d, 3, J = 6 Hz, CH_3), and 8.76 (t, 3, J = 7 Hz, CH_3); mass spectrum m/e (rel intensity) 249 (22), 143 (100).

The 2,4-dinitrophenylhydrazone (**30c**) of **30a** was prepared and recrystallized from methanol, mp 163–165°.

Anal. Calcd for $C_{26}H_{28}O_{12}N_4$: C, 53.06; H, 4.80; N, 9.52. Found: C, 52.82; H, 4.90; N, 9.46.

A 200-mg sample of **29** was ozonized in methanol and worked up in the manner described above to give 330 mg of crude product which showed only a nonpolar spot at R_f ~0.5 (30% ethyl acetate in benzene). From 50% of the crude product, 32 mg of material was isolated by preparative tlc and was assigned structure **30b**: ir 3.67, 5.64, and 5.80 μ; nmr τ 0.03 (s, 1, CHO), 2.53 (d, 1, J = 2.5 Hz, ArH), 2.83 (d, 1, J = 2.5 Hz, ArH), 4.87 (m, 1, CO_2CH), 6.39 (s, 3, CO_2CH), 7.77 (s, 6, $COCH_3$), and 8.86 (d, 3, J = 7 Hz, CH_3); mass spectrum m/e (rel intensity) 249 (11), 129 (100).

2-(6-Acetoxy-10-hydroxy-*trans*-1,6-undecadienyl)-4,6-diacetoxybenzoic Acid μ-Lactone (31).—From the mother liquors **29** there was isolated after several days at room temperature 0.3 g (2%) of fine needles, mp 174–178°. Recrystallization from methanol gave 0.23 g of analytical sample: mp 178.5–180°; uv max 219.5 mμ (ϵ 22,800), 258 (15,900); ir same as ir of **29** except in 10–12-μ region; nmr τ 2.76 (d, 1, J = 2 Hz, ArH), 3.11 (d, 1, J = 2 Hz, ArH), 3.46 (d, 1, J = 15 Hz, =CH), 3.7–4.2 (m, 1, =CH), 4.5–5.0 (m, 2, =CH and COCH), 7.69 (s, 3, $COCH_3$), 7.73 (s, 3, $COCH_3$), and 8.64 (d, 3, J = 6 Hz, CH_3); mass spectrum m/e (rel intensity) 112 (50), 125 (11), 141 (66), 176 (9), 218 (22), 300 (89), 342 (100), 402 (28), 444 (7).

Anal. Calcd for $C_{24}H_{28}O_8$: C, 64.85; H, 6.35. Found: C, 64.59; H, 6.41.

Ozonolysis of 31.—A 167-mg portion of **31** was ozonized and worked up according to the procedure described for ozonolysis

of **29** to give 277 mg of residue which was purified by preparative tlc (30% ethyl acetate in benzene) to yield 96 mg (83%) of an oil that was 95% one spot (R_f 0.35) on tlc. A second preparative tlc of this material did not increase its purity. This material is assigned structure **32** on the basis of its spectral properties: ir 3.67 (twice the strength of the same band in the spectra of **30a**, **30b**), 5.64, and 5.78 μ; nmr τ 0.03 (s, 1, CHO), 0.27 (t, 1, J = 1 Hz CHO), 2.45 (d, 1, J = 2.5 Hz, ArH), 2.73 (d, 1, J = 2.5 Hz, ArH), 4.75 (q, 1, J = 6 Hz, CO_2CH), 7.40 (t, 2, J = 6.5 Hz, CH_2CHO), 7.69 (s, 3, $COCH_3$), 7.71 (s, 3, $COCH_3$), 7.98 (t, 2, J = 6.5 Hz, CH_2), and 8.62 (d, 3, J = 6 Hz, CH_3); mass spectrum m/e (rel intensity) 265 (7), 249 (6), 85 (100).

Registry No.—**1**, 17924-92-4; **2**, 34289-99-1; **4**, 34297-69-3; **5**, 34290-00-1; **6**, 34297-70-6; **7**, 34288-78-3; **8**, 34288-79-4; **10**, 34288-80-7; **11**, 34288-81-8; **12**, 34290-01-2; **13**, 34290-02-3; **15**, 34290-03-4; **16**, 34290-04-5; **17**, 34290-05-6; **18**, 34288-82-9; **19**, 34288-83-0; **20**, 34297-71-7; **20** triacetate, 34297-72-8; **21**, 34290-06-7; **22**, 34290-07-8; **23**, 34290-08-9; **24** α isomer, 29181-06-4; **24** β isomer, 29181-19-9; **24** cis isomer diacetate, 34290-11-4; **24** trans isomer diacetate, 34290-12-5; **25** dimethyl ether, 34290-13-6; **28**, 10513-52-7; **29**, 34290-14-7; **30a**, 34290-15-8; **30b**, 34290-16-9; **30c**, 34290-17-0; **31**, 34290-18-1; **32**, 34290-19-2.

Chemical Modifications of Zearalenone. II

T. B. WINDHOLZ* AND R. D. BROWN

Department of Synthetic Chemical Research, Merck Sharp & Dohme Research Laboratories, Rahway, New Jersey 07065

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Substitution of carboxyl and formyl groups into the aromatic portion of zearalenone is described and the new structures are unambiguously determined. Elimination reactions occurring during Birch reduction are investigated and a mechanism is proposed that accounts for the obtained products and intermediates.

As part of a program directed toward chemical modifications of zearalenone[1] (**1**) we investigated some of its aromatic substitution and elimination products. Available literature data[2] seemed insufficient to predict, with assurance, the outcome of a Kolbe–Schmitt reaction on **1** since the carbonation of resorcinol is described as leading primarily to 2,4-dihydroxybenzoic acid, while a 90% yield of 2,6-dihydroxy-4-methylbenzoic acid had been obtained from 3,5-dihydroxy-1-methylbenzene. Because of the sensitivity of zearalenone, we decided on relatively short reaction times for carbonation, and found that using potassium carbonate at 175° and 800 psi carbon dioxide for 3 hr,[3] a single carboxylic acid **2a** was obtained in better than 50% yield.

Since physical data could not safely distinguish between the two possible positions for the carboxy group in the aromatic ring, chemical degradation had to be undertaken. The sequence of reactions is shown in Scheme I. Successive methylations of the purified Kolbe–Schmitt product with methyl sulfate and diazomethane afforded a dimethoxymethyl ester **2b**, which was submitted to ozonization. It was found best to oxidize immediately the presumed dialdehyde **3** to a crude diacid **4a**, which was esterified to **4b** and purified by chromatography. Hydrolysis of this triester gave a tricarboxylic acid **5a** which was best purified by reesterification to **5b**, chromatography, and renewed hydrolysis to the crystalline triacid. Although the nmr signal for the single aromatic proton at τ 2.6 was a clear indication that it is flanked by a methoxy and a carboxy group [*cf.* the signals at τ 2.8 and 3.25 of the two types of easily identifiable protons in 2,4-dimethoxybenzoic acid (**6**)[4]], we have been able to identify **5a** with an authentic sample[5] of 2,4-dimethoxybenzene-1,3,6-tricarboxylic acid, mp 240–241°.

It was of further interest to determine the structure of a monoformyl derivative **7** of zearalenone, which was obtained by a Friedel–Crafts type formylation.[6] To this end, both the purified formylation product **7** and the carboxylic acid **2a** were converted to the same carboxamide **9** as shown in Scheme I. Since the aldehyde **7** did give a monoxime **8a**, its further conversion to the nitrile **8b** and the corresponding carboxamide **9** did not present difficulties. This carboxamide was found to be identical with the one obtained directly from the methyl ester of acid **2a**, proving that both carboxylation and formylation of zearalenone have occurred at the same carbon atom.

Birch reduction of the aromatic nucleus was investigated using the ethylene ketal **10** of the saturated macrocycle. Reaction with 4 equiv of sodium (the minimum required for significant reduction) in liquid ammonia and *tert*-butyl alcohol afforded two homogeneous, oily products, each in *ca.* 30% yield. Both were rather unstable to conventional manipulations because of a marked tendency to aromatize.

The more polar product, which had retained one methoxy group, was assigned[7] structure **11a** on spectral grounds. On treatment with CrO_3 in pyridine it was converted into the aromatic, noncrystalline ketal **12a**, which was further characterized by acid hydrolysis to 2-(10-hydroxy-6-oxoundecyl)-6-methoxybenzoic acid μ-lactone (**12b**), mp 96–97°, identical in all respects with a sample prepared by methylation of authentic[8] 2-(hy-

(1) For leading references regarding isolation, structure, and total syntheses of this fungal metabolite see paper I: N. P. Jensen, R. D. Brown, S. M. Schmitt, T. B. Windholz, and A. A. Patchett, *J. Org. Chem.*, **37**, 1639 (1972). This paper also describes specifics of physical measurements and standard procedures.

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(3) We thank Dr. W. H. Jones and associates for performing this reaction.

(4) Kindly supplied by Mr. H. L. Slates of these laboratories.

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