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TOTAL SYNTHESIS OF THE MACROLIDE, ZEARALENONE[1]

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Abstract—Total synthesis of the biologically active macrolide zearalenone together with its optical resolution and the determination of its absolute configuration as "S" are described.

Wittig condensation with an ortho aldehydic ester proceeded in part with vicinal interaction and formation of an acetylenic product.

A SUBSTANCE demonstrating pronounced anabolic as well as uterotrophic activity was isolated in 1962 from the fungus *Gibberella zeae* growing as a mould on corn.[2] This substance was subsequently shown by Urry *et al.*[3] in 1966 to be a macrolide with structure **1** and was designated zearalenone, namely, an enone derivative of a resorcylic acid lactone isolated from *Gibberella zeae*.

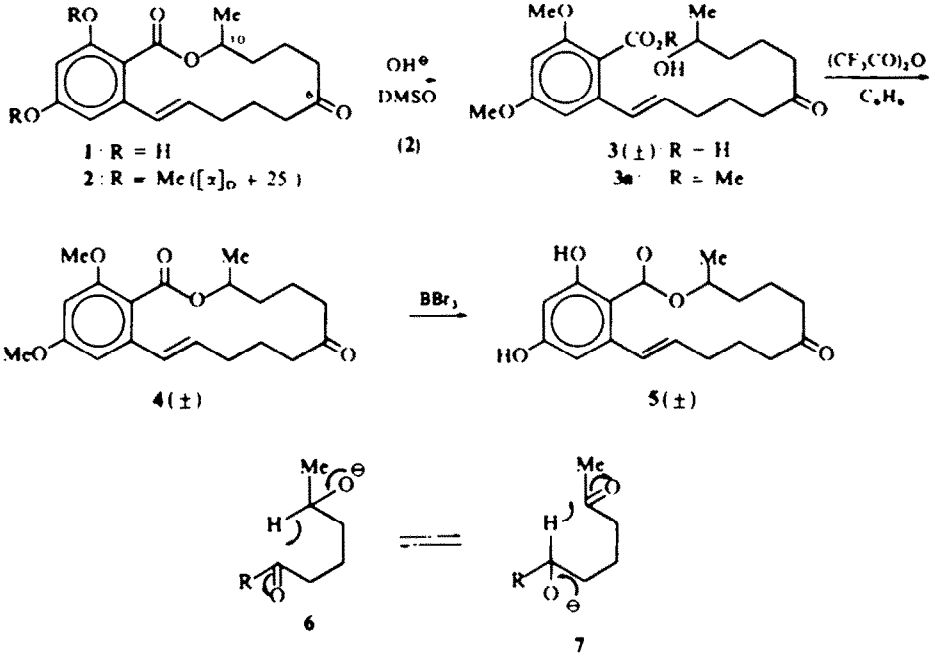
In contemplating a synthesis of zearalenone it was visualized that the penultimate stage would involve the ring closure of a properly functionalized hydroxyacid to its corresponding 14-membered lactone. The final step in turn would require cleavage of appropriate masking substituents on the phenolic functions which in the case at hand were chosen to be methyl ether groupings. To test these final stages of a projected route, zearalenone **1** was converted to its dimethyl ether derivative **2** and the latter was indeed found capable of retrocleavage to zearalenone **1** by means of boron tribromide in methylene chloride at 0°[4] or to a less satisfactory extent with pyridine hydrochloride at 180°.

Hydrolytic cleavage of the lactone grouping of zearalenone dimethyl ether **2** was not possible under normal saponification conditions but proceeded smoothly with sodium hydroxide in refluxing aqueous DMSO to provide an essentially quantitative yield of a *seco* acid product containing **3**. The latter in turn was found to undergo recyclization in part to zearalenone dimethyl ether **4** on low temperature treatment with a benzene solution of trifluoroacetic anhydride.[5,*] The dimethyl ether of zearalenone thus obtained, however, revealed itself to be racemic. The question therefore arose as to whether the product was structurally homogeneous and if the racemization at C-10 had occurred during the saponification step *via* an internal oxidation-reduction† or as a consequence of the trifluoroacetic anhydride-catalyzed

* This procedure has also been applied to the dihydro seco acid producing zearalanone dimethyl ether, and to the tetrahydro seco acid (Experimental).

† Professor Urry in his structure studies on seco-systems derived from zearalenone observed this phenomenon as measured by deuterium exchange at positions alpha to C-10. (Private communication). See also Ref. 3

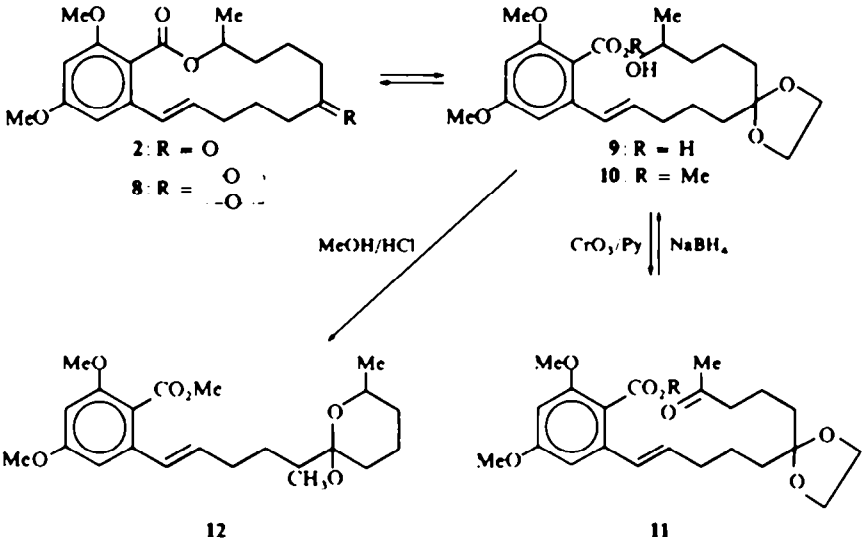
ring closure. It is noteworthy in this connection that the inactive seco acid **3** exhibited no CH_3—C=O in its NMR spectrum as would have been anticipated from an equilibration of the type **6** ⇌ **7**. Despite this NMR result, however, later findings (see below) established unequivocally the non-homogeneity of **3** relative to carbon atoms 6 and 10.



The following sequence demonstrated that the racemization had indeed occurred during the saponification step. Zearalenone dimethyl ether **2** was converted to its ethylene ketal derivative **8** and the latter saponified to the seco acid ketal **9**. This compound as its methyl ester **10** possessed an optical rotation of $[\alpha]_D^{MeOH}$ +5·6°. Recyclization of active **9** *via* **3** with trifluoroacetic anhydride regenerated zearalenone dimethyl ether **2** with a rotation of $[\alpha]_D$ +25° identical with material derived from natural zearalenone by methylation; the ORD curves of these two samples were also identical. It was thereby established that alkaline cleavage of the lactone ring of **2** is indeed accompanied by internal disproportionation (**6** ⇌ **7**) leading to racemization. Oxidation on the other hand of the seco ester ketal **10** with chromic anhydride in pyridine provided the ketone **11** (NMR δ 2·12 (s), MeCO). The latter on reduction with sodium borohydride afforded racemic seco ester ketal **10** which on saponification followed by acid removal of the ketal function provided an authentic, structurally homogeneous sample of racemic seco acid **3**.

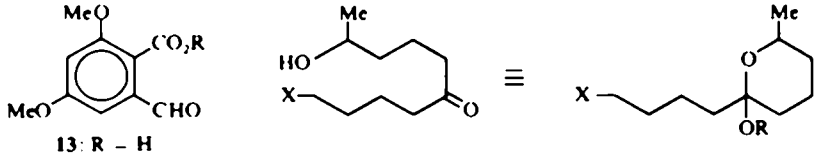
Cyclization of **3** yielded racemic zearalenone dimethyl ether **4** in turn cleaved to (±) zearalenone **5** m.p. 187–189°.

As stated earlier, although the NMR spectrum failed to indicate a Me $\underset{|}{C}$=O

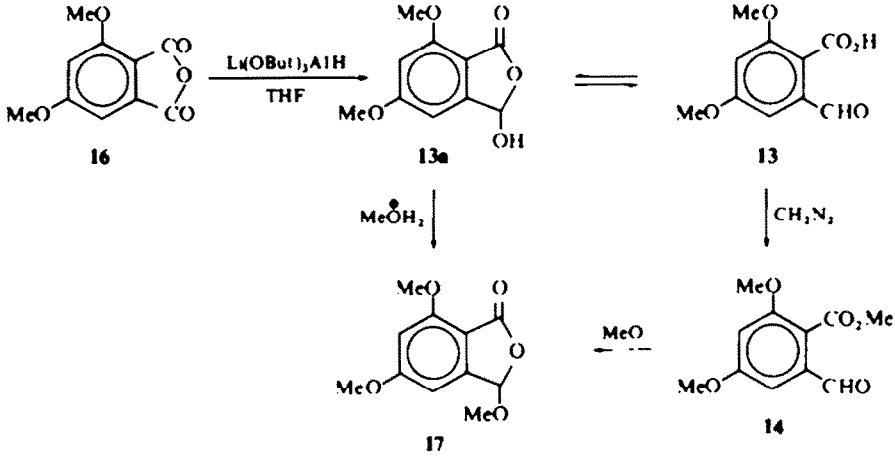


group in the disproportionated seco acid derived by direct saponification of zearalenone dimethyl ether, the presence of isomeric species conforming to an equilibrium product (**6** ⇌ **7**) was observed from a subsequent transformation. Thus, the seco ester ketal **10** which is structurally homogeneous, was converted with methanol and hydrogen chloride to the cyclic methyl ketal **12**. The latter exhibited a doublet methyl in its NMR spectrum in pyridine-d_5 at δ 1·12 (d, J = 6·0 c/s) and a single aliphatic methoxyl at δ 3·18 in agreement with expectations based on **12** as well as with the corresponding NMR spectrum of this structural moiety derived from the total synthetic series (see below). By contrast the seco ester **3a** derived *via* direct alkaline cleavage of zearalenone dimethyl ether (not previously ketalized at C-6) afforded a product which in the NMR exhibited a doublet at δ 1·12 (J = 6 c/s) and singlet at δ 1·27 in the Me region as well as 2 bands in the aliphatic OMe region at δ 3·18 and 3·21. These observations substantiate the presence of two structural types best accommodated by the isomers arising from 6-keto-10-hydroxy and 6-hydroxy-10-keto-species.

At this juncture, the feasibility of lactone ring closure of the seco acid as well as subsequent ether cleavage to zearalenone having been established, we turned our attention to the total synthesis of the seco acid **3** itself. To this end the seco acid was depicted as a two component system joined by a double bond in which the one component is the aromatic system, 2-formyl-4,6-dimethoxybenzoic acid **13** whereas the second component is the aliphatic moiety **15** in which the functionality at C-6 and C-10 may be mutually masked *via* internal ketal formation.

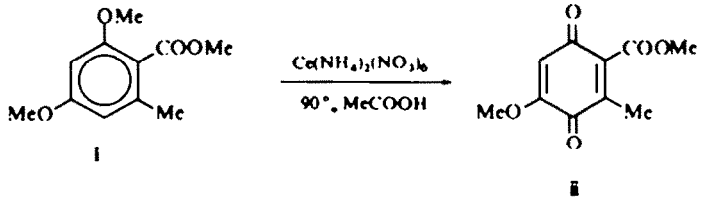


The aromatic component, 2-formyl-4,6-dimethoxybenzoic acid **13**, had been obtained previously from natural product sources only, namely from the bitter principle isolated from mouldy carrots[6] and from zearalenone by ozonolysis.[3] Total synthesis of this individual was accomplished by reduction of the known 3,5-dimethoxyphthalic anhydride **16**[7] with lithium tri-t-butoxyaluminum hydride in tetrahydrofuran at 20°.[8,*] Material obtained in this manner, m.p. 193–196°, was identical with 2-formyl-4,6-dimethoxybenzoic acid derived from zearalenone by ozonolysis. This phthalaldehydic acid like similar systems[9] of this type exists in solution entirely in the hydroxyphthalide form **13a** as evidenced by IR maxima at 3·15 and 5·65 μ as well as the absence of aldehydic H and carboxyl H in the NMR spectrum. Urry *et al.*[3] had previously shown that this substance reacts with methanolic hydrogen chloride to give the methoxyphthalide **17**. In contrast thereto and in conformity with recent findings[10] in a parallel instance, **13** reacts with diazomethane in tetrahydrofuran solution to give almost exclusively the open aldehydic ester **14**. Treatment of the latter on the other hand with a catalytic amount of sodium methoxide, in methanol–dimethyl sulfoxide leads smoothly to the cyclic isomer **17**.† Normal ester **14** was also obtained by ozonization of (±) seco acid methyl ester **3a**.



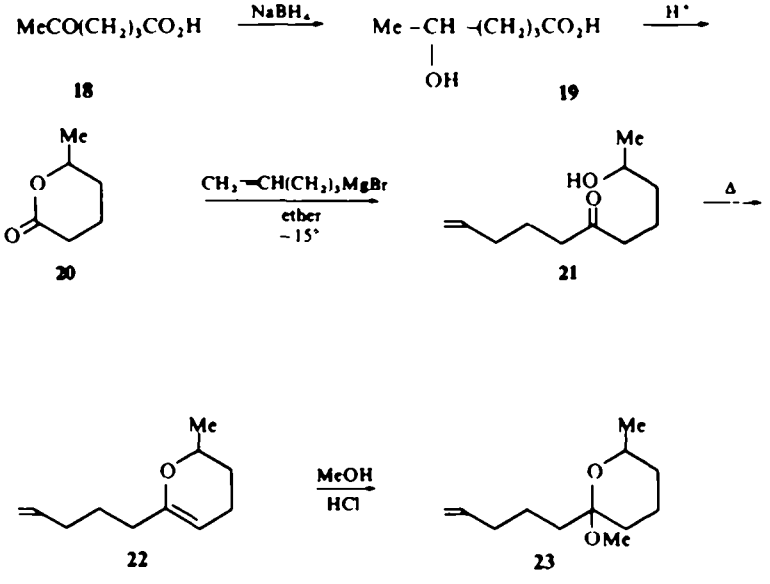
* In the present case the reagent attacks exclusively the sterically favored CO group. The reaction mixture also contained 5,7-dimethoxyphthalide (over-reduction) and 3,5-dimethoxyphthalic acid (Experimental). For an alternative synthesis of **13** see ref 1c.

In another approach to **13** Ce^{4+} oxidation of **i** was examined. cf. L. Syper, *Tetrahedron Letters* 4493, (1966). However, the only isolable produce was 2-methyl-3-carbomethoxy-5-methoxyquinone **ii**, m.p. 70–73°



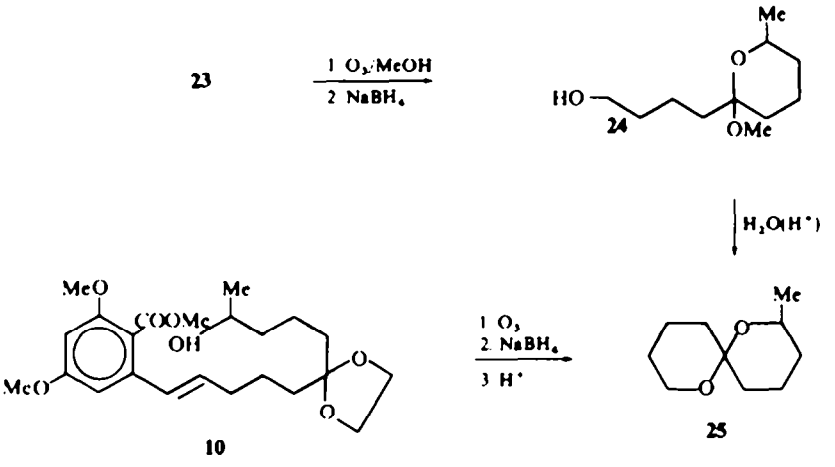
† The formation of cyclic ester **17** from normal ester **14** with methoxide anion provides structural analogy for Bender's mechanism for the saponification of *o*-formyl benzoate esters.[11]

Synthesis of the aliphatic component **15** proceeded from 5-ketohexanoic acid **18**. This acid was converted in 85–90% yield to 5-hydroxyhexanoic acid lactone **20** by reduction of the former with sodium borohydride to 5-hydroxyhexanoic acid **19** followed by acidification and distillation. Treatment of this lactone at −15° in ether solution with 4-pentenylmagnesium bromide permitted the separation of the 1:1 reaction product as a complex. Acidification of the latter followed by distillation under reduced pressure produced the cyclic enol ether **22** in over 50% yield, λ_{max} 5·98 μ (—O—CH=), 6·09 (CH_2=CH—). Isolation of the Grignard product prior to distillation revealed its constitution to be largely the open hydroxyketone **21** with strong bands in the IR at 3·02 μ (OH) and 5·88 μ (C=O). Either component **21** or

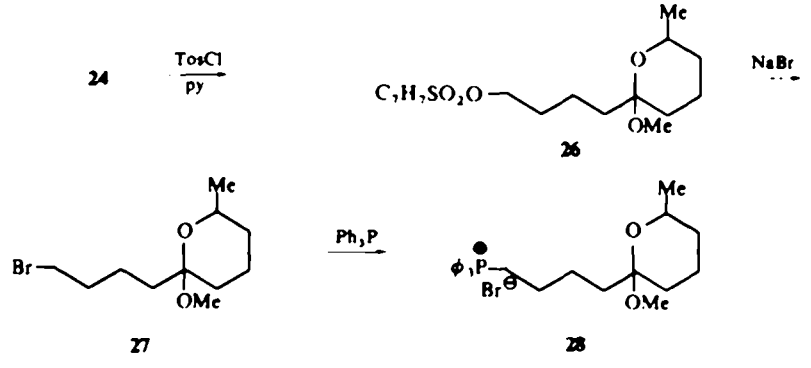


22 could be converted essentially quantitatively to the cyclic methyl ketal **23** with 1% hydrogen chloride in methanol. The lability of both **22** and **23** was demonstrated by their respective rapid reversal to acyclic hydroxy ketone **21** when their deuteriochloroform solutions were treated with deuterium oxide. Trace amounts of DCl presumably were present. The NMR spectrum of **23** exhibited the expected doublet methyl at δ 1·13 and singlet methoxyl at δ 3·17 and thus provided an authentic reference for comparison with samples of seco ester ketal **12** previously discussed.

Ozonolysis of **23** at −60° in methanol followed by sodium borohydride reduction of the intermediate ozonide provided the carbinol **24**. The lability of this carbinol was quite spectacular in that its deuteriochloroform solution on treatment with deuterium oxide caused almost instantaneous conversion to the spirane **25**. The latter was also produced from (±) methyl ester ethylene ketal **10**, derived from zearalenone. This sequence provides synthetic identification–comparison of the aliphatic segment of the zearalenone molecule.



The carbinol **24** was converted to its tosylate derivative **26** with *p*-toluenesulfonyl chloride in pyridine and thence to the corresponding bromide **27** with sodium bromide in refluxing methanol. The latter was converted in turn with triphenylphosphine in hot methanol to the phosphonium bromide **28** isolated in analytically pure although non-crystalline form. In the several steps including tosylate formation, the cyclic ketal grouping suffered cleavage to a greater or lesser degree under the pertinent reaction conditions to the corresponding acyclic hydroxyketone species. This fact, however, constituted no obstacle since the cyclic ketal system was easily

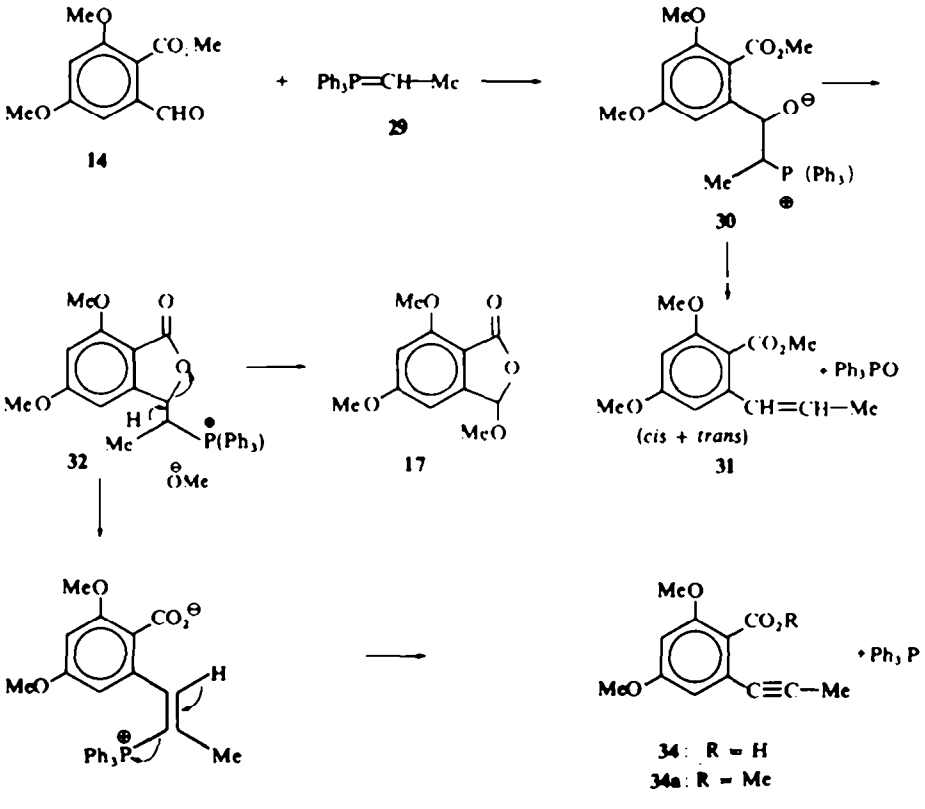


reformed on contact with methanol and anhydrous hydrogen halide. In actuality the reconstitution of the cyclic ketal was only of compelling importance at the phosphonium salt stage anticipatory to phosphorane formation.

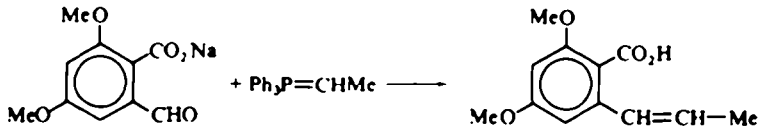
Before engaging in the Wittig-coupling of the aromatic (**14**) with the aliphatic (**28**) component, the reaction of **14** with a model phosphorane was studied. This was prompted out of consideration of the proximity of the neighboring carboxyl function

and the profound influence it might be anticipated to exercise on the course of the Wittig reaction.

The aldehyde ester **14**, therefore, was allowed to react in dimethyl sulfoxide with ethylidene triphenyl phosphorane **29** prepared by the sodium hydride-dimethyl sulfoxide technique.[12] The red solution of the phosphorane retained its color for an extended period of time and was only dissipated in large measure after ca. 48 hr. The reaction product yielded an acidic as well as a neutral fraction. From the neutral fraction was isolated in addition to triphenylphosphine oxide also triphenylphosphine together with ca. 20% each of the expected olefin **31** and the methoxy phthalide **17**. The latter could arise from intermediate **32** by methoxide displacement of ethylidene triphenylphosphorane **29**—thereby accounting for the long retention of the red ylid color. However, if the reaction of **14** with **29** were slow relative to release of methoxide ion from betaine **30** (**30** → **32**), then **17** could alternatively be formed by reaction of methoxide with **14** as discussed earlier. The acidic fraction yielded a crystalline substance m.p. 132–136° with mol. wt. 220 (mass spec.) exhibiting triple bond absorption in the infrared at 4·50 μ. This substance proved to be the acetylenic acid **34** presumed to arise together with triphenylphosphine from sequential elimination *via* the intermediates **32** and **33**.



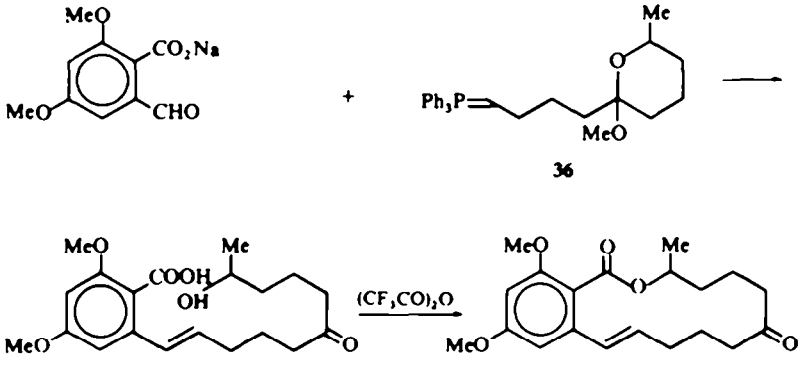
In contrast to the complex reaction course observed with the aldehydic ester **14**, the Wittig-coupling with the sodium salt of the acid **13** proceeded rapidly and in a straightforward manner to yield the propenyl acid **35** in ca. 60% yield.



35

This acid **35** like the corresponding ester was a cis-trans mixture in the ratio of 35:65 respectively. Fusion of this acid mixture with potassium hydroxide, according to the method of its formation from the carrot factor,[6] permitted the isolation of *trans* **35** in crystalline form m.p. 85–88° identical with that reported by Sondheimer.[6,*]

The phosphonium salt **28** corresponding to the aliphatic component was converted to its ylid **36** with sodium hydride in DMSO. Treatment of this ylid with the sodium salt of **13** in DMSO caused immediate discharge of the red color of the ylid solution. The product on work-up provided 55–60% of a mixture of *cis* and *trans*



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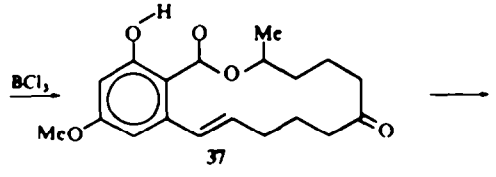
3 **4**



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2-l-Menthoxyacetate derivative $[\alpha]_D^{CHCl_3} - 39°$ $\xrightarrow[2\ BBr_3]{1\ OH}$ **1**

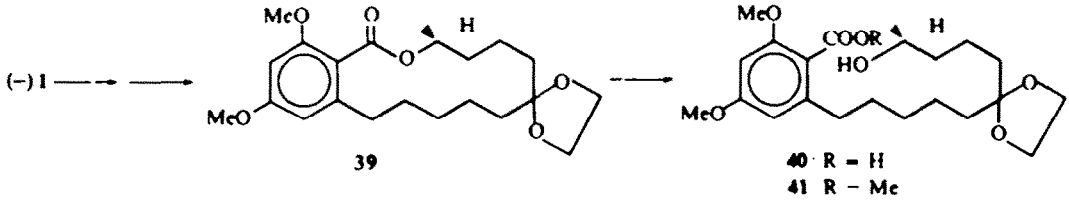
38

* The CO region of the solution IR spectra of acids **34** and **35** was anomalous in that *two* equally prominent bands were present (5·80, 5·90 μ), both of which were absent in the spectra of the corresponding salts. The 5·80μ band may be attributed to the monomeric form present in greater equilibrium concentration than normal because of steric hindrance to dimerization.

(±) seco acids 3. The NMR of the methyl ester of synthetic 3 exhibited a doublet methyl ester peak at δ 3·90 and 3·95 in a ratio of 1:1 corresponding to the effect of the aliphatic side chain *cis* and *trans* respectively on the ester chemical shift. Conversion of synthetic 3 to the cyclic methyl ketal derivative corresponding to 12 permitted analysis by VPC and established the cis-trans ratio, in conformity with NMR findings, at 48:52 respectively. For another route to (±) 3 see ref. 1*d*.

Ring closure of the *cis-trans* mixture of seco acids 3 provided (±) zearalenone dimethyl ether 4, m.p. 124–126°. The latter on selective ether cleavage with boron trichloride in methylene chloride[13] yielded the 4-monomethylether 37 which was resolved *via* the 2-l-menthoxyacetate 38 $[\alpha]_D^{Chf}$ −39°. Mild saponification of 38 to (−) 37 and cleavage of the latter with boron tribromide led to (−) zearalenone 1 m.p. 157–159° $[\alpha]_D^{Chf}$ −190° identical in all respects with the natural product.

Finally, the absolute configuration of (−) zearalenone was determined as "S" by application of Horeau's method[14] to the dihydro seco acid methyl ester ethylene ketal 41. The latter was obtained by diazomethane treatment of the crystalline seco acid ketal 40, in turn derived from 39 by the sodium hydroxide-aqueous dimethyl sulfoxide procedure described above.



EXPERIMENTAL

M.ps were taken on a microscope hot-stage apparatus and are uncorrected. UV spectra were determined in MeOH on a Cary model 11 PMS spectrometer and IR spectra on a Perkin-Elmer Infracord instrument. NMR spectra were recorded on a Varian A-60 spectrometer using TMS as an internal standard. Optical rotations were measured with a Zeiss photoelectric polarimeter employing a 0·5 decimeter tube and ORD were determined on a Cary Model 60 recording spectropolarimeter. TLC was carried out on silica gel G coated glass plates and column charomatography on silica gel H columns by the "dry column" technique.* The proper elution system was determined by TLC probes, and fractions were collected automatically.

(±) 2-(10-*Hydroxy-6-oxo-1-undecenyl*)4,6-*dimethoxybenzoic acid* 3

To a stirred soln of 10 g of (+) 2[3] in 100 ml DMSO maintained under N_2 was added over 5 min 60 ml 20% NaOH aq. The resulting red soln was refluxed gently for 2 hr (internal temp ~120°). The mixture was cooled to 10–15°, acidified with dil HCl and extracted 4 times with $CHCl_3$. The $CHCl_3$ extract was in turn extracted with dil $KHCO_3$ aq. The latter extract was washed once with $CHCl_3$ and acidified with dil HCl. The acidified mixture was extracted with $CHCl_3$ and the latter extract washed with sat NaCl aq, dried over $MgSO_4$ and concentrated to dryness under vacuum. Crude seco acid 3 was obtained (10·2 g) as a pale yellow viscous oil, $[\alpha]_D^{Chf}$ 0; λ_{max}^{MeOH} 295 (1900), infl 255 (11,000) 223 mμ (23,000); λ_{max}^{Chf} 3·0–3·4, 5·82, 5·88 μ; NMR ($CDCl_3$) δ 1·17 (d) J = 6 c/s $\underline{CH_3}$—$\underset{|}{\overset{|}{C}}$—H, 3·85 (s)—Me, 3·89 (s)—Me, 7·07 (s) 2 active H position concentration dependent disappeared on adding D_2O. In other runs varying minor amounts of another Me doublet δ 1·23 (J = 6) was present.

* Procedure of T. E. Beesley of these Laboratories.[15]

In a probe run attempted saponification of 2 utilizing 10% NaOH aq in aqueous MeOH gave only a few per cent of acidic material after 24 hr of reflux.

(±) Zearalenone dimethyl ether **4** *from* (±) **3**

To a stirred soln of 10·0 g (27·5 mmol) of crude (±) **3** in 2800 ml benzene under N_2 and cooled to 10° was added over 1 hr 20 ml (29·4 g, 140 mmol) of trifluoroacetic anhydride. The cooling bath was removed and after an additional hr 5% NaOH aq was added with stirring and external cooling until the mixture was basic (~200 ml). The layers were separated, the aqueous layer was extracted twice with benzene, and the combined benzene layers washed twice with water, once with sat NaCl aq, dried over $MgSO_4$ and concentrated to dryness under vacuum to give 7·03 g of neutral dark-colored gum. Work up of the basic extract gave 1·3 g of recovered **3** with NMR spectrum similar to that of starting acid.

Crystallization of the neutral material from ether gave 200 mg crude **4** mp 117–123°. Chromatography of the mother liquors on 150 g silica gel H, elution with 4% acetone–$CHCl_3$ (~5 ml fractions), and crystallization of the pertinent fractions from ether gave 1·06 g pure **4** (conversion yield 15%)* mp 124–126°; $[\alpha]_D^{CHCl_3}$ ±0°; ORD (MeOH ±0°). (Found: C, 68·94; H, 7·44. Calc. for $C_{20}H_{26}O_5$: C, 69·34; H, 7·57%.)

The TLC mobility, IR, UV and NMR spectra were identical with the respective properties of **2**.

(+) Zearalenone dimethyl ether **2** *from seco acid ketal* **9**

To a stirred soln of 0·90 g of (+) **9** in 5 ml THF was added 5 ml 2·2N perchloric acid. After 2 hr at room temp 50 ml water was added and the mixture extracted with $CHCl_3$. The $CHCl_3$ extract was washed with sat NaCl aq and dried over $MgSO_4$. Removal of the solvent under vacuum gave 700 mg of (+) seco acid **3**.

To a stirred soln of 688 mg (1·88 mmol) of the above acid in 200 ml benzene at 6° under N_2 was added 0·27 ml (0·40 g, 1·90 mmol) trifluoroacetic anhydride. The pale yellow soln was kept at 6° for 18 hr. The reaction mixture was extracted with cold 4% KOH aq, washed with NaCl aq and dried over $MgSO_4$. Removal of the solvent under vacuum gave 234 mg neutral material which crystallized on trituration with ether to afford 200 mg (80% conversion yield) of (+) **2** mp 107–110°; $[\alpha]_D^{MeOH}$ +25°. This material was identical with authentic **2**, mp 108–110°, $[\alpha]_D^{MeOH}$ +25° by mixed m.p., IR, ORD and TLC criteria.

Acidification of the KOH extract and $CHCl_3$ extraction gave 400 mg of recovered **3** with identical IR spectrum as starting (+) **3**. Likewise the IR spectrum of the derived **12** was identical with that of an authentic sample.

Zearalenone dimethyl ether ethylene ketal **8**

A mixture of (+) zearalenone dimethyl ether (10·0 g) *p*-toluenesulfonic acid (525 mg) in ethylene glycol (75 ml) and toluene (450 ml) was gently refluxed with slow azeotropic distillation of the formed water. After 4 hr the Zimmerman test for α-methylene ketones was negative. The mixture was cooled, the layers separated and the aqueous phase extracted with ether. The combined organic extract was washed with 5% $NaHCO_3$ aq, sat NaCl aq, dried over $MgSO_4$ and concentrated to dryness under vacuum. Crystallization of the residue from ether–hexane gave **8**, 10·9 g (94%) m.p. 101–103°; λ_{max}^{MeOH} 298 mμ (ε 2210), 253 mμ (ε 12,850) and 223 mμ (ε 32,000). (Found: C, 67·51; H, 7·75. Calc for $C_{22}H_{30}O_6$: C, 67·67; H, 7·74%.)

1-(3,5-Dimethoxy-6-carboxyphenyl)10-hydroxy-1-undecene-6-ethyleneketal **9**

By the procedure utilized to obtain (±) **3** from **2** a soln of **8** (25 g) in 300 ml DMSO and 188 ml 20% NaOH aq was refluxed 2 hr. Work up as in the preparation of (±) **3** gave 25·1 g of **9** as a pale yellow oil, $\lambda_{max}^{CHCl_3}$ 2·85–3·2, 5·82, 6·06, 6·25, 6·35, 6·89, 8·6, 9·52, 10·32, 10·50, 10·70 μ.

(+)1-(3,5-Dimethoxy-6-carbomethoxyphenyl)10-hydroxy-1-undecene-6-ethyleneketal **10**

Compound **9** (4·75 g) in 25 ml distilled THF was esterified with excess diazomethane in ether. Concentration of the reaction mixture gave hydroxy methyl ester ketal as an oil (4·92 g); $[\alpha]_D^{MeOH}$ +5·6°; $\lambda_{max}^{CHCl_3}$ 2·85, 2·98, 5·81, 6·06, 6·24, 6·33, 6·88, 7·00, 7·56, 7·90, 8·13, 8·32, 8·60, 9·05, 9·50, 10·31, 10·50, 10·68 μ.

NMR ($CDCl_3$) δ 1·18 (d) J = 6 c/s CH_3–$\overset{|}{C}$–H, 3·80, 3·82, 3·89 (3—Me singlets), 3·95 (s) 4H —O CH_2CH_2—O

* The conversion yield of lactone was greatly improved when the molar ratio of trifluoroacetic anhydride to seco acid was decreased from 5:1 to 1·1 and the reaction run at 6° for 18 hr (see the following experiment).

1-(3,5-*Dimethoxy-6-carbomethoxyphenyl*)10-*oxo*-1-*undecene*-6-*ethyleneketal* **11**

A soln of **10** (5·0 g; 12 mmol) in 35 ml pyridine was added dropwise (30 min) at 15° to a stirred mixture of CrO_3 complex in pyridine,[16] prepared from 3·57 g CrO_3 and 35 ml pyridine. After 16 hr at room temp the reaction mixture was poured into ice water and extracted with ether. The ether extract was washed with water, NaCl aq, dried over $MgSO_4$ and concentrated under vacuum to give **11** (4·70 g) as a pale yellow oil: $\lambda_{max}^{CHCl_3}$ 5·82 5·85 (broad), 6·06, 6·25, 6·32, 6·89 μ; NMR ($CDCl_3$) δ 2·12 (s) MeCO, 3·81, 3·86, 3·88 (3 Me singlets), 3·93 (s) 4H O CH_2CH_2 O.

(±) 1-(3,5-*Dimethoxy-6-carbomethoxyphenyl*)10-*hydroxy*-1-*undecene*-6-*ethyleneketal* **10** *by reduction of* **11**

Powdered $NaBH_4$ (2·0 g) was added in portions to a stirred soln of **11** (4·70 g) in 100 ml MeOH at 0°. After 1 hr at room temp water was added and most of the MeOH was removed by concentration under reduced press. The mixture was extracted with ether and the latter extract washed with water, dried over Na_2SO_4 and concentrated to dryness under vacuum to give (±) **10** (4·7 g); the IR spectrum in $CHCl_3$ was essentially the same as that of optically active **10**.

(±) 2-*Methoxy*-6-*methyl*-2-*pent*-4-*enyl*-5[2-(1-*carbomethoxy*-4,6-*dimethoxyphenyl*] *tetrahydropyran* **12**

A soln of 1% methanolic HCl (8 ml) was added dropwise to a stirred soln of (±) **10** in 3 ml MeOH. After 16 hr at 20° powdered $NaHCO_3$ was added followed by ether and water. The organic phase was washed with water, dried over Na_2SO_4 and concentrated under vacuum to give (±) **12** (818 mg) as a pale yellow oil. The analytical sample was freed from minor polar impurities by preparative TLC ($CHCl_3$, EtOAc 7:3); R_f in this system = 0·35; NMR (C_6D_5N) δ 1·12 (d) J = 6 c/s CH_3 · C H; 3·18 (s) aliphatic OMe, 3·72, 3·80, 3·95 (3 singlets) ester and aromatic OMe. (Found: C, 67·03; H, 8·23. Calc. for $C_{22}H_{32}O_6$: C, 67·32; H, 8·22%.)

(+)2-*Methoxy*-6-*methyl*-2-*pent*-4-*enyl*-5[2-(1-*carbomethoxy*-4,6-*dimethoxphenyl*] *tetrahydropyran* **12** *from* (+) **10**

Treatment of (+) **10** (2·11 g) with 1% methanolic HCl (15 ml) by the procedure utilized for (±) **10** gave 2·17 g of **12**; TLC $CHCl_3$–EtOAc-single spot same mobility as (±) **12**. A sample (365 mg) was molecularly distilled at 200°/0·5 mm. Total material distilled to give a colorless oil. (Found: C, 67·61; H, 7·98; Calc. for $C_{22}H_{32}O_6$: C, 67·32; H, 8·22%.)

Cyclic methyl ketal product from crude (±) *seco acid* **3**

(±) Seco acid **3** (2·0 g) derived *via* direct saponification of (+) **2** in 10 ml THF was converted to methyl ester by addition of ethereal diazomethane. A 200 mg sample of this methyl ester was converted to cyclic **12** by treatment as above with methanolic HCl. NMR ($CDCl_3$) δ 1·12 (d) J = 6 c/s; 1·27 (s); 3·18, 3·21, 3·80, 3·90. In addition to the bands due to **12**, there were present bands at δ 1·27 and 3·21 indicative of the presence of ~40% of an isomeric species—e.g. the 10-methoxy isomer of **12**.

(±) 1,7-*Dioxa*-2-*methyl*-*spiro*[5,5]*undecane* **25** *from ozonization of* **10**

A soln of (±) **10** (1·23 g) in 80 ml anhyd MeOH was ozonized at −35° until the effluent gas gave a positive starch iodide test. Excess O_3 was removed with a N_2 stream. Powdered $NaBH_4$ was added at −30° to the stirred soln and the mixture was kept at 0° for 1 hr and at 25° for 0·5 hr. The solvent MeOH was removed under vacuum, water was added and the mixture extracted with benzene. The benzene extract was washed with water, dried over Na_2SO_4 and concentrated to dryness under vacuum to give 426 mg of crystalline residue m.p. 134–142° $\lambda_{max}^{CHCl_3}$ 5·68 μ, identified as crude 5,7-*dimethoxyphthalide*. Crystallization from MeOH gave pure material, m.p. 148–151° (reported[17]) m.p. 151–153°.

The combined aqueous extracts were acidified with 2·5N HCl and extracted with ether. The ether extract was washed with water dried over Na_2SO_4 and concentrated under vacuum to give 475 mg of crude **25** containing a minor amount of phthalide. This material was purified by short path distillation; volatile camphoraceous colorless oil, IR and NMR spectra identical with the respective spectra of material obtained by acid treatment of **24**. (Found: C, 70·53, H, 10·50. Calc. for $C_{10}H_{18}O_2$: C, 70·54; H, 10·66%.)

2-*Formyl*-4,6-*dimethoxybenzoic acid*(3-*hydroxy* 5,7-*dimethoxyphthalide* **13**, **13a**

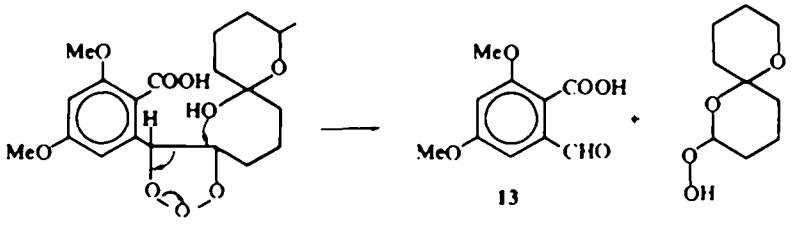
(A) *Reduction of* 3,5-*dimethoxyphthalic anhydride*. A soln of 5·10 g (20·0 mmol) lithium tri t-butoxy aluminium hydride in 60 ml THF was added over 30 min to a stirred soln of 4·16 g 3,5-dimethoxyphthalic

anhydride[8] in 60 ml THF at 10°. The colorless soln was kept 18 hr at room temp. It was then concentrated to dryness on the water pump and EtOAc and cold dil HCl added. The mixture was extracted 5 times with EtOAc, the latter extract washed with NaCl aq, dried over $MgSO_4$ and concentrated to dryness under vacuum. Trituration of the semi-crystalline residue with acetone gave 670 mg of **13** m.p. 184–189°; single spot on TLC ($CHCl_3$: EtOAc : AcOH-5 : 4 : 1). Crystallization from acetone–ether gave the analytical sample as prismatic needles, m.p. 193–196° (reported[6] m.p. 190–196°); λ_{max} 295 (5510), 258 (12,900), 214 mμ (26,400) λ_{max}^{THF} 3·15 (strong), 5·65 μ (strong); NMR (pyridine d_5) δ 3·79 (6H singlet) 5,7-OMe, 6·61 (d) J = 2 c/s, 6·95 (d) J = 2 c/s -- 4,6-H; 6·90 (broad s) 3-H, (similar spectrum in acetone d_6); NMR (1·5N NaOD in D_2O) δ 9·54 (s) aldehyde H. (Found : C, 57·17; H, 4·68. Calc. for $C_{10}H_{10}O_5$: C, 57·14; H, 4·80%.)

The mother liquors contained additional **13** as well as 5,7-dimethoxyphthalide, 3,5-dimethoxyphthalic acid and anhydride as indicated by TLC ($CHCl_3$: EtOAc : AcOH-5 : 4 : 1). In another run the total yield of **13** formed was determined to be 33% by reaction of an aliquot of the product (667 mg) with 2,4-dinitrophenylhydrazine in MeOH–H_2SO_4 aq to give 415 mg of **13** 2,4-dinitrophenylhydrazone, m.p. 235–240° (reported[6] 237–244°).

(B) *Ozonization of* (±) *seco acid* **3**. A soln of 5 grams of (±) **3** derived *via* saponification of **2** in 100 ml MeOH at −30° was treated with O_3 until one molar equiv O_3 had been absorbed. During the reaction a heavy ppt formed. The cold reaction mixture was treated with 7 ml, Me_2S[10] and allowed to stand at room temp for 4 hr. The solvents were removed *in vacuo* and the residue was taken up in EtOAc. The EtOAc soln was extracted several times with $NaHCO_3$ aq. Acidification of the bicarbonate extracts afforded, after extraction with EtOAc and concentration *in vacuo*, 2·10 g of **13**, m.p. 186–191°.

In another run (10 g of ±**3**) the ppt which formed during the ozonization was filtered washed with cold (−70°) MeOH and dried in air (2·8 g m.p. 184–186°). It proved to be **13**, possibly formed *in situ* by assisted cleavage of the primary ozonide as indicated.



Methyl 2-formyl-4,6-dimethoxybenzoate **14**

(A) *Methylation of* **13**. Diazomethane generated from N-methyl-N-nitroso-p-toluene sulfonamide was swept by a gentle N_2 stream into a soln of 400 mg of **13** in 10 ml THF. After 30 min excess diazomethane and solvent were removed under vacuum. The solid residue was crystallized from acetone–ether to give **14**, m.p. 85–87°; λ_{max} 327 (1840), 264 (3920), 207 mμ (23,000); $\lambda_{max}^{CS_2}$ 3·70 (weak), 5·79, 5·86 μ; NMR ($CDCl_3$) δ 3·85, 3·87, 3·96 (3-3H singlets · OMe, 6·73 (d) J = 2 c/s, 6·99 (d) J = 2 c/s – 2-aromatic H, 10·0 (s) aldehydic H. (Found: C, 59·23; H, 5·28 : Calc. for $C_{11}H_{12}O_5$: C, 58·92; H, 5·40%.)

(B) *Ozonization of* **3a** (±) Seco ester **3a** (7 g) on ozonization in 180 ml MeOH at −30° followed by Me_2S work up as described for the ozonization of **3** gave 2·06 g of **14** m.p. 79–84°, raised to 85–87° on crystallization from ether. A 14 g ozonization worked up by filtration of the intermediate ppt (as described above), gave after crystallization of the crude product from ether–hexane, 3·8 g of **14** m.p. 85–86°.

3,5,7-*Trimethoxyphthalide* **17**

To a stirred soln of 206 mg (0·92 mmol) methyl 2-formyl-4,6-dimethoxybenzoate in 10 ml DMSO was added 0·25 ml 0·44N NaOMe in MeOH (0·11 mmol NaOMe). After 75 min TLC (5% acetone in $CHCl_3$) of an aliquot indicated complete conversion to **17** (single spot). Water was added to the mixture which was then extracted 4 times with $CHCl_3$. The latter extract was washed with water, sat NaCl aq, dried over $MgSO_4$ and concentrated to dryness under vacuum. Crystallization of the residue (210 mg) from aqueous EtOH gave prisms m.p. 119–121° (reported[3] 117 119°). On crystallization from ether needles m.p. 91–93° were obtained. λ_{max} 295 (6140), 258 (13,600), 213 mμ (27,100); $\lambda_{max}^{CS_2}$ 5·69 μ; NMR ($CDCl_3$) δ 3·59 (s) · 3-OMe,

3·92, 3·96 (2 singlets) —5,7-OMe, 6·13 (s) —3-H, 6·51 (d) J = 1·5 c/s, 6·60 (d) J = 1·5 c/s — 4,6-H. (Found: C, 59·17; H, 5·41. Calc. for $C_{11}H_{12}O_5$: C, 58·92; H, 5·40%.)

Reaction of aldehyde ester **14** *with ethylidene triphenylphosphorane*

To a stirred soln of 1·85 g (5·00 mmol) ethyl triphenylphosphonium bromide in 15 ml DMSO maintained under N_2 was added 3·45 ml 1·45N methyl sulfinyl carbanion (5·0 mmol) in DMSO.[12] After 20 min a soln of **14** (1·12 g, 5 mmol) in 15 ml DMSO was added during 5 min to the stirred deep red orange ethylidene triphenylphosphorane soln. The colour faded to yellow over 48 hr at which time water was added and the weakly basic mixture extracted with ether. The ether extract was washed with NaCl aq, dried over $MgSO_4$ and concentrated to dryness to yield 1·19 g neutral gum. The aqueous extract on acidification with dil HCl and $CHCl_3$ extraction gave 740 mg acidic material as a cream colored foam. Trituration of the neutral product with ether–hexane gave triphenylphosphine oxide, m.p. 151–153° on recrystallization from ether. The filtrate was concentrated to dryness and chromatographed on 21 g silica gel H (dry column). Elution with 5% acetone in $CHCl_3$ gave 3 identified substances. In order of increasing polarity these were: triphenyl phosphine m.p. 75–77° (identical mobility and IR spectrum as authentic material); *methyl-2-prop-1-enyl-4,6-dimethoxybenzoate* **31** (210 mg), pale yellow oil, λ_{max} 295 (2430), 253 (11,300), 225 mμ (25,000); $\lambda_{max}^{CHCl_3}$ 5·82, 6·07 (weak), 10·35 μ (strong); NMR ($CDCl_3$) δ 1·86 (*d*) J = 4 c/s Me —CH=, 3·79, 3·81, 3·88 (3-OMe), 5·96–6·60 (4H multiplet) and 3,5,7-*trimethoxyphthalide* **17** (150 mg) m.p. 119–121° (from aqueous EtOH) identical with an authentic sample. VPC analysis of **31** indicated two main components (*cis, trans*) (area ratio ~30:70).

Dry column chromatography of the acidic extract (740 mg) on 25 g silica gel H and elution with $CHCl_3$–EtOAc–AcOH 5:4:1 (3 ml fractions) gave 200 mg of essentially single spot *2-prop-1-ynyl-4,6-dimethoxybenzoic acid* **34**, prisms from acetone–ether, m.p. 132–136°; λ_{max} 303 (3100), 297 infl. (2970), 251 (11,000), 218 mμ (33,000); $\lambda_{max}^{CHCl_3}$ 4·50 (weak), 5·78 (strong), 5·89 (strong), both CO bands were absent in the spectrum of the Na salt; NMR ($CDCl_3$) δ 2·07 (s) Me C≡, 3·81, 3·87 (6H) 2-OMe, 6·45 (d) J = 2 c/s, 6·63 (d) J = 2 c/s–2 aromatic H, 10·75 (s) COOH (Found: C, 65·34; H, 5·12, mass peak 220. Calc. for $C_{12}H_{12}O_4$: C, 65·44; H, 5·49%; mol wt 220·2.)

Propynyl acid **34** with diazomethane in ether–THF gave *methyl 2-prop-1-ynyl-4,6 dimethoxybenzoate* **34a** m.p. 84–88°), $\lambda_{max}^{CHCl_3}$ 4·50 (weak), 5·80 μ (Found: C, 66·65; H, 6·31. Calc. for $C_{13}H_{14}O_4$: C, 66·65; H, 6·02%.)

Reaction of **13** *with ethylidene triphenylphosphorane*-cis *and* trans *2-prop-1-enyl-4,6-dimethoxybenzoic acid* **35**

To the stirred ylid soln prepared from 1·85 g (5·00 mmol) ethyl triphenylphosphonium bromide under N_2 as in the preceding experiment was added, over 5 min a soln of 1·05 g (5·00 mmol) 2-formyl-4,6-dimethoxybenzoic acid in 15 ml DMSO and 3·55 ml (5·00 mmol) 1·41N methylsulfinyl carbanion in DMSO. The soln color lightened from deep red to orange within 15 min. After 2 hr the reaction mixture was added to cold water and neutral material (triphenylphosphine oxide, 55% yield, m.p. 148–153° from ether) removed by ether extraction. The aqueous filtrate was acidified with dil HCl and extracted with $CHCl_3$. The latter extract was washed with sat NaCl aq, dried over $MgSO_4$ and concentrated to dryness under vacuum to give **35** as a colorless viscous oil 643 mg (58%). The NMR spectrum ($CDCl_3$) indicated a 2 component mixture: 2 sets of split doublets δ 1·73 (J = 7 and 2 c/s), 1·88 (J = 6 and 2 c/s) area ratio ~35:65 (3H)-*cis*: *trans* MeCH=CH—, 3·85 (s), 3·88 (s), 3·92 (s) 6H OMe, 5·75–7·05 (m) 4H-aromatic and vinyl H, and 10·35 (broad s) —COOH.

A 280 mg aliquot of this product was ground with 850 mg powdered KOH and the mixture kept at 180–185° for 1 hr.[6] Water and dil HCl were added to the cooled mixture, which was then extracted with ether. The ether extract was washed with sat NaCl aq, dried over $MgSO_4$ and concentrated to dryness under vacuum. Crystallization of the residue from ether–hexane gave *trans* **35** m.p. 85–88° (105 mg); reported[6] 85–87°; λ_{max} 298 (2150), infl. 255 (11,700), 223 mμ (26,400); $\lambda_{max}^{CHCl_3}$ 5·80, 5·90, 10·36 μ; in morpholine the 5·80 and 5·90 bands were absent; NMR ($CDCl_3$) split doublet δ 1·90 (J = 6 and 2 c/s) 3H *trans* MeCH=CH—, 3·85 (s) 3·90 (s) 6H —OMe, 5·80–7·05 (m) 4H-aromatic and vinyl H, 10·65 (broad s) COOH. (Found: C, 64·77; H, 6·33; Calc. for $C_{12}H_{14}O_4$: C, 64·85; H, 6·35%.)

A 100 mg aliquot of the Wittig product (*cis, trans* **35**) was converted to the corresponding **31** with diazomethane in ether. VPC analysis indicated a 2 component mixture with area ratio 33:67 in agreement with the NMR findings on *cis, trans* **35**.

(±) *Zearalenone* 5

To a stirred soln of 480 mg of (±) 4 in 5 ml CH_2Cl_2 under N_2 at 0° was added a cooled (0°) soln of 2·0 ml (5·2 g) of BBr_3 in 3 ml CH_2Cl_2. The mixture was immediately concentrated to dryness under water pump vacuum (bath temp 30°). The solid residue was triturated with water and the ppt filtered, washed with water and dried under vacuum to give 641 mg crude product. This material was triturated with 8 ml 10% acetonitrile in $CHCl_3$ (76 mg did not dissolve) and the filtrate chromatographed on 25 g silica gel H eluting with the same solvent system (2 ml fractions). The fractions of nearly single spot 5 were combined (148 mg, 34%) and crystallized from nitromethane to give (±) zearalenone as prismatic needles (96 mg, 22%) m.p. 188–190°. The IR and UV spectra were identical with the respective spectra of (−) zearalenone. (Found: C, 67·53; H, 6·83. Calc. for $C_{18}H_{22}O_5$: C, 67·90; H, 6·97%.)

(−) *Zearalenone* 1

(A) *Boron tribromide treatment of* (−) 37. To a stirred soln of 100 mg of (−) 37 in 1 ml CH_2Cl_2 at 0° was added 0·4 ml (1·1 g) BBr_3 in 1 ml CH_2Cl_2 at 0°. The reaction mixture was immediately concentrated to dryness and worked up as described for the preparation of (±) zearalenone. The residue was purified by preparative TLC (10% acetonitrile in $CHCl_3$) to give 56 mg (59%) of single spot 1. Crystallization from nitromethane gave a first crop of 30 mg of 1 m.p. 157–159°, undepressed on admixture with (−) zearalenone of m.p. 157–159°. The respective IR and UV spectra and ORD curves were identical.

(B) *Boron tribromide treatment of* (+) *zearalenone dimethyl ether* 2. By the procedure utilized to convert (±) 4 to (±) 5, 120 mg of 2 was converted to 36 mg of single spot 1, m.p. 157–159° on crystallization from nitromethane.

(C) *Pyridine hydrochloride treatment of* (+) *zearalenone dimethyl ether* 2. (+) Zearalenone dimethyl ether (500 mg) and 5 g pyridine hydrochloride were mixed and kept at 180° for 1 hr under N_2. The mixture was cooled, dil HCl added and the organic material extracted into CH_2Cl_2. The latter extract was washed with sat NaCl aq dried over $MgSO_4$ and concentrated to dryness under vacuum. TLC ($CHCl_3$ 2·5% acetonitrile) indicated the product to be a complex mixture containing zearalenone. The latter was isolated by preparative TLC. Crystallization from acetone–hexane gave material m.p. 154–158°, undepressed on admixture with (−) 1 m.p. 157–159°.

(−) *Zearalenone 4-methyl ether-2-(1)-menthoxyacetate* 38

A. From (−) 37. (1)-Menthoxyacetyl chloride (0·6 ml) was added dropwise to a stirred soln of (−) 37 (250 mg) in 1·7 ml dry dioxan and 1·1 ml dry pyridine and the reaction mixture was stirred at 25° for 4 hr. Water was then added and the product was extracted into benzene. The latter extract was washed with HCl aq, water, 5% $NaHCO_3$ aq, sat NaCl aq, dried over $MgSO_4$ and concentrated to dryness under vacuum. Crystallization of the red oily residue from acetone–pet. ether gave 321 mg of (−) 38, m.p. 118–121°. Recrystallization from the same solvent mixture provided the analytical sample, m.p. 123–125°; $[\alpha]_{max}^{CHCl_3}$ −38·5°; ORD λ^{MeOH} 400 mμ (−500°), 350 (−1000°), 300 (−3000°), 278 (φ, −7000°), 268 (0°); λ_{max}^{MeOH} 257 (12,300), 240 (20,600), 234 mμ (22,100); $\lambda_{max}^{CHCl_3}$ 5·60, 5·86, 6·20, 6·38, 6·88, 6·98, 7·80, 8·15, 8·90, 9·05, 9·55 μ.

B. *From* (±) 37. 1-Menthoxyacetyl chloride (0·67 ml) was added dropwise to a stirred soln of (±) 38 (278 mg) in 1·9 ml dioxan and 1·2 ml pyridine under N_2, and the mixture stirred at 25° for 4 hr. Work up as above (A) led to a red oil which crystallized spontaneously on standing in MeOH–ether to give (−) 38 (28 mg) m.p. 121–123°, no depression on mixed m.p. with (−) 38 prepared under A. The respective optical rotation, ORD curves, IR and UV spectra were identical. (Found: C, 69·92; H, 8·29. Calc. for $C_{31}H_{44}O_7$: C, 70·43; H, 8·39%.)

Dry-column chromatography of the mother liquors led to 360 mg crystalline material, fractional crystallization of which was unsuccessful in providing additional resolved 38.

(±) *Zearalenone 4-methyl ether* 37

To a stirred soln of 496 mg of (±) 4 in 4 ml CH_2Cl_2 at −28° was added rapidly 1·7 ml (2·4 g) BCl_3 in 4 ml CH_2Cl_2 (t = −28°). The reaction mixture was immediately poured onto ca. 50 g crushed ice and extracted with CH_2Cl_2. The latter extract was washed with water, sat NaCl aq, dried over $MgSO_4$ and concentrated to dryness to give 402 mg (85%) of nearly single spot 37. Crystallization from MeOH gave

300 mg m.p. 108–111°; IR and UV spectra identical with the respective spectra of (−) **37**. (Found: C, 68·84; H, 7·12; Calc. for $C_{19}H_{24}O_5$: C, 68·65; H, 7·27%.)*

(−) *Zearalenone 4-methyl ether* **37**

A. *From (+) zearalenone dimethyl ether* **2**. By the procedure of the preceding experiment 5·0 g of (+) **2** was converted into 3·76 g of (−) **37** m.p. 118 120° (from MeOH) (reported[3] m.p. 120–122°); IR and UV spectra identical with the respective spectra of an authentic sample.

B. *From* (−) **38**. Compound (−) **38** (60 mg) in MeOH (1·2 ml) was saponified with 2·5N NaOH (0·3 ml) at 25° for 2 hr. The reaction mixture was acidified with cold 2·5N HCl and extracted with $CHCl_3$. The latter extract was washed with 5% $NaHCO_3$ aq, water, sat NaCl aq, dried over $MgSO_4$ and concentrated under vacuum to give 40 mg crystalline (−) **37** m.p. 114–116°, undepressed on admixture with an authentic sample. The respective IR spectra were identical.

5-Hydroxyhexanoic acid lactone **20**

To a stirred soln of 13·014 g (0·1 mol) of **18** in 80 ml water containing 10·082 g (0·12 mol) $NaHCO_3$ at 0° was added portionwise 1·89 g (0·05 mol) $NaBH_4$. The resulting reaction mixture was stirred at room temp for 4 hr and then cautiously made acidic with HCl to pH 2. After 19 hr at room temp the reaction mixture was saturated with NaCl and extracted with ether. The ether extract was washed with sat. NaCl aq and dried over Na_2SO_4. Evaporation of ether followed by distillation afforded 9·528 g (83·5%) of **20**, b.p. 112–113°/21 mm (lit.[19] b.p. 107°/14 mm).

2-(*Pent-4-enyl*) 6-*methyl*-Δ^2-*dihydropyran* **22** *and* 10-*hydroxy*-1-*undecene*-6-*one* **21**

An ethereal soln of 4-pentenylmagnesium bromide[20] prepared from 35·397 g (0·2375 mol) 1-bromo-4-pentene and 7·296 g (0·3 mol) Mg in 130 ml ether, was added dropwise to a stirred soln of 27·108 g (0·2375 mol) 5-hydroxyhexanoic acid lactone in 300 ml ether at −15° over 2 hr under an atmosphere of N_2. The heterogeneous reaction mixture was stirred at −10° for another ½ hr and decomposed with sat NH_4Cl aq. The aqueous layer was extracted with ether. The combined ether layers were in turn extracted with 5% NaOH aq, sat NH_4Cl aq and NaCl aq respectively. After drying over Na_2SO_4 and removal of ether followed by distillation there was afforded 20·363 g (51·5%) of **22**, b.p. 52–54°/0·65 mm; λ_{max}^{Film} 3·31, 5·98, 6·09, 10·92 and 13·12 μ, NMR ($CDCl_3$) δ 1·26 (d, J = 6·5 c/s, H–C–CH_3); 3·93 (m, O–C–H), 4·47 (broad triplet, O–C=C–H), 5·05 (m, –CH=CH_2) and 5·75 (m, –CH=CH_2). The NMR spectrum changed on addition of D_2O exhibiting a signal at 1·18 (d) due to a secondary Me group and a broad multiplet at 3·78 (O–C–H); the broad triplet due to O–C=C–H was absent. The compound, when recovered from the NMR sample, showed bands at 3·02 and 5·88 μ in its IR spectrum and consequently was **21**.

2-(*Pent-4-enyl*) 2-*methoxy*-6-*methyltetrahydropyran* **23**

To a stirred sample (15·3 g, 0·092 mol) of **22** at 0° was added 40 ml 1% methanolic HCl. With the addition of the first 1 ml the temp of the reaction mixture rose to 50°. It was cooled to 25° and the rest of the methanolic HCl was added at that temp. After 3·5 hr excess solid $NaHCO_3$ was added to the reaction mixture. After stirring for 15 min at room temp the reaction mixture was filtered to remove inorganic material, the filtrate evaporated at 30° *in vacuo* and finally distilled to yield 16·218 g (88·8%) of **23**; b.p. 57–59°/0·6 mm; λ_{max}^{Film} 3·30, 6·09 and 10·9 μ, NMR ($CDCl_3$), δ 1·13 (d, J = 6·5 c/s, H–C–CH_3); 3·17 (s, OMe). Found: C, 73·13; H, 11·33. Calc. for $C_{12}H_{22}O_2$: C, 72·68; H, 11·18%.)

* It was our experience that sequential cleavage of zearalenone dimethyl ether, initially at C-2 with BCl_3 and finally at C-4 with BBr_3, was a substantially better process than direct BBr_3 cleavage of both ether functions affording zearalenone in an overall yield of 50–55%.

2-(δ-Hydroxybutyl) 2-methoxy-6-methyltetrahydropyran **24** *and 1,7-dioxa-2-methyl-spiro[5:5]undecane* **25**

A slow stream of 3% O_3 was passed through a soln of 9·915 g (0·05 mol) of **23** in 100 ml MeOH at ~ −60° until the reaction mixture was saturated with O_3.

The excess ozone was removed in a stream of N_2 and solid $NaBH_4$ (9·45 g, 0·25 mol) was added slowly to the reaction mixture at such a rate that the temp of the latter did not exceed 0°. After stirring for ½ hr at 0° and 1½ hr at room temp, the MeOH was removed at ~40° *in vacuo*. Water was added to the semi-solid residue and the organic material extracted with ether. The ether extract was washed with water, dried over Na_2SO_4 and finally evaporated to yield 9·13 g (92%) of **24**. λ_{max}^{Film} 3·05 μ NMR ($CDCl_3$) δ 1·15 (d, J = 6·5 c/s, H–C–$\underline{CH_3}$); δ 3·46 (s, OMe). The NMR spectrum changed on addition of D_2O. The compound when recovered from $CDCl_3$–H_2O after 15 hr had quantitatively changed to **25**. It did not show absorption in the OH region in its IR spectrum. Its NMR spectrum in $CDCl_3$ displayed a 3 proton-multiplet centered at δ 3·71 and a doublet at δ 1·12 (H–C–$\underline{CH_3}$); no signal due to OMe group was present. It was identical in its IR and NMR spectra with the aliphatic material obtained from ozonolysis of (±) **10** followed by $NaBH_4$ treatment.

2-(δ-p-Toluenesulfonyloxybutyl) 2-methoxy-6-methyltetrahydropyran **26**

To a stirred soln of 8·526 g (0·4214 mol) of **24** in 40 ml dry pyridine at 0° was added 16·205 g (0·085 mol) *p*-toluenesulfonyl chloride under an atm of N_2. The clear soln immediately became heterogeneous due to the separation of pyridine hydrochloride. After 17 hr at 5° the reaction mixture was poured into an ice–water mixture (250 ml) containing 38·64 g (0·46 mol) $NaHCO_3$. After stirring for 1½ hr the reaction mixture was extracted with ether. The ether extract was washed with 5% $NaHCO_3$ dried over Na_2SO_4 and evaporated at ~40° *in vacuo* to yield 12·945 g (86·2%) of **26** as a viscous oil; λ_{max}^{Film} 6·27, 7·38 and 8·48 μ; NMR ($CDCl_3$) δ 1·09 (d, J = 6·5 c/s H–C–$\underline{CH_3}$), 2·43 (s, =C–Me), 3·09 (s, O–Me), 4·04 (t, CH_2–CH_2–OSO_2–) 7·33 and 7·79 (each broad doublet; 2-aromatic hydrogens). The product as described above was sometimes accompanied by varying amounts of enol ether and hydroxy ketone forms, the latter two forms were readily convertible almost entirely to the tetrahydropyran form by treatment of the entire product with 1% HCl-MeOH.

2-(δ-Bromobutyl) 2-methoxy-6-methyltetrahydropyran **27**

A stirred soln of 9·368 g (0·02628 mol) of **26** and 55 ml dry MeOH containing 6·761 g (0·0657 mol) NaBr was gently refluxed for 5 hr under an atm of N_2. A fine ppt of NaBr appeared immediately after the refluxing had started. It redissolved in 1 hr and thereafter crystalline sodium *p*-toluenesulfonate was deposited. The solvent was removed *in vacuo* and the residue treated with ether and filtered. The filtrate was evaporated to yield an oily material which after treatment with 1% HBr–MeOH followed by solid Na_2CO_3 gave 6·752 g of **27**. The latter did not show the presence of the starting material in its IR and NMR spectra.

α-(2-Methoxy-6-methyltetrahydropyran-2-yl) butyltriphenyl phosphonium bromide **28**

A soln of 3·975 g (0·015 mol) of **27**, 4·338 g (0·0165 mol) triphenylphosphine in 30 ml dry MeOH was refluxed for 20 hr under an atm of N_2. Most of the MeOH was evaporated at ~40° *in vacuo* and to the residue was added dry benzene to precipitate the phosphonium bromide. The benzene layer was decanted off, the residue was washed with more benzene and finally evaporated to a light yellow foam. In order to convert a small amount of the hydroxy ketone form of the phosphonium bromide present in the product to the tetrahydropyran form, the material was treated with 30 ml 1% HBr MeOH for 3 hr at room temp. An ethereal soln of diazomethane was added to decompose the excess HBr and finally the reaction mixture was evaporated to yield 5·211 g (65·9%) of **28** as a foam; $\lambda_{max}^{CHCl_3}$ 6·30, 6·98, 8·98 and 14·45 μ; NMR ($CDCl_3$) δ 1·04 (d, J = 6·5 c/s H–C–$\underline{CH_3}$), 3·09 (s, OMe), 7·75 (center of multiplet due to aromatic protons).

(Found: C, 66·28; H, 7·08; Br, 15·45. Calc. for $C_{29}H_{36}O_2PBr$: C, 66·03; H, 6·88; Br, 15·15%.)

2-(10-*Hydroxy*-6-*oxo*-1-*undecenyl*) 4,6-*dimethoxybenzoic acid* **3**

To a stirred soln of 4·972 g (0·00942 mol) of **28** in 12 ml DMSO was added 4·01 ml of a 2·35 molar soln of methyl sulfinyl carbanion[12] in DMSO at 0° under an atm of N_2. The deep red soln was stirred at room temp for 10 min and to this was added sodium 2-formyl-4,6-dimethoxybenzoate (prepared by adding 4·01 ml of 2·35 molar soln of methylsulfonyl carbanion in DMSO to 1·981 g (0·00942 mol) of **13**, in 10 ml DMSO whereby the red color of ylid **36** was immediately decolorized. After 15 hr at room temp the reaction mixture was added to water and the neutral material removed by extraction with ether. The aqueous layer was made acidic with dil HCl and extracted with ether. The organic layer was extracted with 5% $NaHCO_3$ aq, the alkaline layer made acidic with dil HCl and finally extracted with ether. The latter extract was washed with water, dried over Na_2SO_4 and evaporated to yield 1·892 g (55·1%) of **3** as a gum. $\lambda_{max}^{CHCl_3}$ 2·8–4·3, 5·81, 5·88, 6·24 and 10·31 μ. This synthetic sample of **3** was found to be a mixture of *cis* (48%) and *trans* (52%) isomers; this ratio was arrived at by VPC and NMR studies of the cyclic methyl ketal derivative of the methyl ester of **3** obtained by its successive treatment with diazomethane and 1% HCl–MeOH. The NMR spectrum of the totally synthetic **12** was very instructive especially in the OMe region. It exhibited 6 well-defined peaks in that area, the assignment of which with reasonable certainty could be made by comparison with the NMR spectrum of pure *trans* **12**. The chemical shift (δ 3·71 or 3·78) of OMe protons at position **4** was different from that due to the 2-OMe hydrogens but again was independent of the *cis* and *trans* nature of the compound. The remaining two OMe's gave rise to 4 peaks (δ 3·14, 3·17, 3·90, 3·95); two corresponding to *cis* and two due to the *trans* isomer. Integration of the area of the two peaks at δ 3·90 and 3·95 (CO_2CH_3) indicated the ratio of *cis* and *trans* isomers to be of the same order as obtained by VPC analysis.

(±) *Zearalenone dimethyl ether* **4** *from synthetic* **3**

To a stirred soln of 0·911 g of synthetic **3** in 300 ml dry benzene at ~12° was added 2·8 ml trifluoroacetic anhydride over a period of 15 min under an atm of N_2. After 1½ hr at 12° 10% NaOH aq was added until the reaction mixture was basic. The layers were separated, the alkaline layer was extracted with benzene and the combined benzene layers washed with water, dried over Na_2SO_4 and evaporated to yield 0·475 g gummy neutral material. Chromatography of the latter on 20 g silica gel H, followed by elution with 5% acetone $CHCl_3$ and crystallization of the pertinent fractions from ether–n-hexane gave 0·090 g of ± **4** identical in every respect with the sample derived from a similar cyclization of (±) **3** which in turn had been obtained by alkaline hydrolysis of (±) zearalenone dimethyl ether.

The acidic material obtained from the alkaline layer was essentially starting material as shown by its TLC and IR spectrum. No attempts were made to ascertain the ratio of *cis* and *trans* isomers in the recovered acid.

(+) 1-(3,5-*Dimethoxy*-6-*carboxyphenyl*-10-*hydroxyundecane*-6-*ethylene ketal* **40**

By the procedure utilized to obtain (±) **3** from **2** a soln of **39**[21] (1·00 g) in 10 ml DMSO and 6 ml 20% NaOH aq was refluxed 3·5 hr. The mixture was cooled, water added and it was extracted with $CHCl_3$. The latter extract was washed with water, dried over $MgSO_4$ and concentrated to dryness under vacuum to give 400 mg of recovered **39** m.p. 88–90°. The original aqueous basic layer was acidified with 2·5N HCl and extracted with $CHCl_3$. The latter extract was washed with water, dried over $MgSO_4$ and the solvent removed under vacuum to give 650 mg of **40** which crystallized on trituration with ether hexane, m.p. 63–67°. $[\alpha]_D^{CHCl_3}$ +7·4°, $\lambda_{max}^{CHCl_3}$ 2·8–3·3, 5·85–5·88 μ; NMR ($CDCl_3$) δ 1·18 (d) J = 6 c/s CH_3–$\underset{i}{C}$–H, 3·82, 3·87 (2-OMe singlets), 3·92 (s) 4H –OCH_2CH_2O–. (Found: C, 64·33; H, 8·56. Calc. for $C_{22}H_{34}O_7$: C, 64·38; H, 8·35%.)

1-(3,5-*Dimethoxy*-6-*carbomethoxyphenyl*) 10-*hydroxyundecane*-6-*ethylene ketal* **41**

To a soln of 55 mg of **40**, m.p. 63–67° in 5 ml ether was added excess distilled diazomethane in ether. After 15 min the soln was taken to dryness under vacuum leaving **41** as a colorless oil (56 mg); TLC (5% acetone in $CHCl_3$) R_f 0·2-single spot; $[\alpha]_D^{CHCl_3}$ +3·0°; $\lambda_{max}^{CHCl_3}$ 2·80, 2·90 (–OH), 5·80 μ (ester C=O).

Determination of absolute configuration of **41** *by the Horeau procedure*[14]

To 50 mg (0·12 mmol) of **41** in 0·7 ml pyridine was added 73 mg (0·24 mmol) α-phenylbutyric anhydride.[22] After 18 hr at room temp water and benzene were added and the mixture was extracted several times with

0·2N Na_2CO_3. The basic extract was washed several times with ether, acidified with 6N HCl and extracted with benzene. The benzene extract was washed with water, dried over $MgSO_4$ and concentrated to dryness under vacuum. The residue (44 mg) had IR and NMR spectra identical with those of racemic α-phenylbutyric acid; $[\alpha]_{578}$ −4·8°; $[\alpha]_{546}$ −5·8°; $[\alpha]_{365}$ −17° (C-2, 93-benzene); $[\alpha]_{589}$ −4·5° (extrapolated); minimum optical yield 14% assuming 100% esterification yield. Since the recovered α-phenylbutyric acid was levorotatory, **41** has the "S" configuration at its asymmetric center.

2-(10-Hydroxy-6-oxoundecanyl) 4,6-dimethoxybenzoic acid

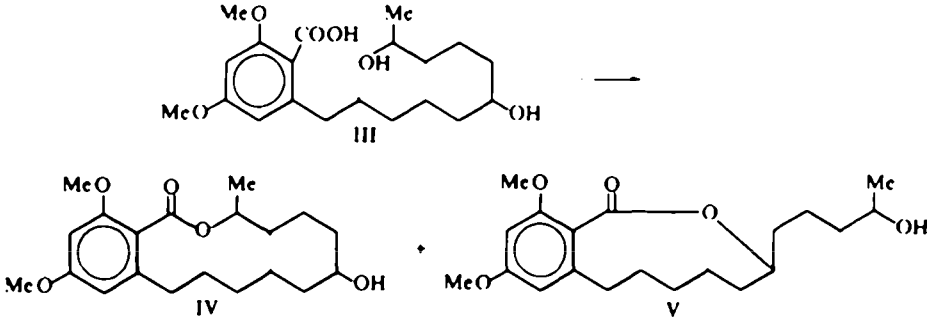
A soln of 550 mg of **40** in 4 ml THF and 4 ml 2N perchloric acid was kept 90 min at room temp. Water was added and the mixture was extracted with $CHCl_3$. The latter extract was washed with water, dried over $MgSO_4$ and concentrated to dryness to give dihydro seco acid (500 mg) as a colorless oil; NMR ($CDCl_3$) δ 1·18 (d) J = 6 c/s $CH_3\,\underset{|}{C}\,-H$, 3·83, 3·88 (2-OMe singlets), 6·20 (broad s) 2 active H disappeared on D_2O equilibration, 6·38 (s) 2H-aromatic. The ketal band at δ 3·92 (compare **40**) was absent.

Zearalanone dimethyl ether

To a stirred soln of 450 mg (1·23 mmol) dihydro seco acid in 150 ml benzene at 5° was added 320 mg (1·5 mmol) trifluoroacetic anhydride. After 2 hr at 10° and 17 hr at 4° the mixture was extracted with cold 4% KOH aq. The aqueous layer was washed with benzene, and the combined benzene soln washed with water, sat NaCl aq dried over $MgSO_4$ and taken to dryness under vacuum. The neutral residue (61 mg) crystallized spontaneously from acetone–ether to give 40 mg zearalanone dimethyl ether, m.p. 129–131° (undepressed on mixed m.p. with an authentic sample). The respective IR spectra were identical.

Acidification of the original basic extract and $CHCl_3$ extraction gave 303 mg of recovered dihydro seco acid *

* The tetrahydro seco acid iii (m.p. 93–95°) derived from zearalanol dimethyl ether iv (m.p. 90–93°) cyclized to give both possible lactones iv and v in roughly equivalent yield, as determined by oxidation ($Na_2Cr_2O_7$–dil H_2SO_4, ether), and isolation of the respective ketones.



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