

# Determination of the Conformation of *E* and *Z* Zearalenone and Their 7 $\alpha$ - and 7 $\beta$ -Hydroxy Congeners<sup>†</sup>

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**Abstract.** The CD spectra of some resorcylic acid macrocyclic lactones (RAL) are reported. The spectra of the *E,Z*-isomeric ketones **1,6** are very similar in shape and magnitude. The Cotton effects of the 7 $\alpha$ -alcohols **2** and **7** are also of the same shape, but the  $\Delta\epsilon$  values of **7** are only ca. 50% of those of the others. The *E*-7 $\beta$ -ol **3** gives a completely different CD, whereas in the *Z*-series **8** shows a similar CD curve as **6** and **7**, but with again reduced magnitude. The CDs of the acetates **4** and **5** are very similar to those of the corresponding alcohols **2** and **3**, resp. The effect of the 7 $\alpha$ - and 7 $\beta$ -hydroxy or acetoxy group on the absolute conformation of the "chain" from C(5) to C(10) is thus transmitted to the absolute value of the torsional angle of the inherently chiral chromophore C(11)-C(12)-C(12a)-C(1a)-C(=O)O in **2,3** and **4,5**, resp. The CD spectra of the *E,Z*-isomers do not exhibit straightforward correlation with the configuration around the C=C double bond.

## INTRODUCTION

$\alpha$ -Zearanol **9**, the dihydro product of ketone **1**, is used as growth promoting factor in ruminants<sup>1,2</sup>. More recently it has been found that its *Z*- $\alpha$ -congener **7** has similar biological activity as **2**<sup>3,4</sup>. Therefore we investigated the chiroptical data of the *E,Z* as well as  $\alpha,\beta$ -isomers, in order to examine the effect of the configurational change on the conformational properties of the macrocyclic ring. Since all these derivatives were prepared by non-enzymatic reactions from **1**, the (*3S*) stereochemistry remains unchanged. The absolute configuration at C(7) follows from the X-ray diffraction studies of 5-hydroxy-zearalenone<sup>5</sup> and  $\alpha$ -zearalenol<sup>6</sup>, and from chemical correlation of the

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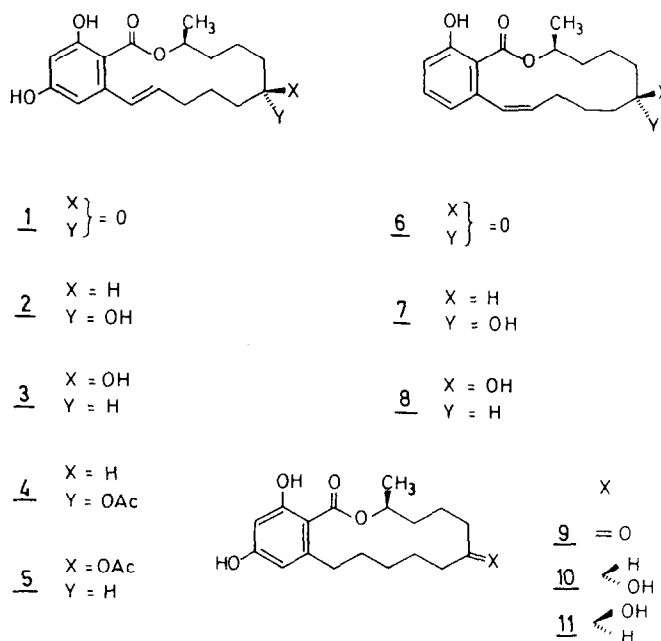
<sup>†</sup>Dedicated to Prof. Dr. K. Schaffner, on the occasion of his 60th birthday

other products with them. The *E*-configuration is also established for natural zearalenone **1** and its congeners<sup>5,6</sup>. Photochemical isomerization of the *E*-isomers leads to the corresponding *Z*-isomers<sup>7</sup>. Since thus the absolute configuration of all investigated compounds is known, we made use of CD spectroscopy to determine their preferred conformation in solution.

## RESULTS AND DISCUSSION

### *The CD spectra of $\alpha,\beta$ -isomers with E-configuration.*

With our new equipment it was possible to record the CD spectrum of ketone **1** down below 190 nm, revealing an additional shoulder at 205 nm ( $\Delta\epsilon = -5$ ), and another negative Cotton effect at ca. 193 nm ( $\Delta\epsilon = -31$ ). All other values coincide practically with those already published<sup>8</sup>. The <sup>13</sup>C-NMR data obtained in the meantime<sup>9</sup> are for **1-3** in best agreement with the conclusions drawn from our CD study<sup>8</sup>, and those of the X-ray diffraction.



The CD of **2** resembles that of **1** not only qualitatively, but also quantitatively, confirming thus that the absolute conformation of the absorbing moiety is very similar for both molecules (Figure 1). This is in agreement with the just mentioned NMR data, which, however, refer to the non-absorbing part of the macrocyclic ring. A molecular model shows also that a  $7\alpha$ -OH does not introduce any particular steric hindrance. On the other hand, the epimeric  $7\beta$ -alcohol **3** shows a completely different CD spectrum (Figure 1), in which the Cotton effects have either opposite signs or at least very unlike  $\Delta\epsilon$ -values as compared to those of **2**. By this aforementioned type of interaction the chain from C(5) to C(10) has to adopt a quite different conformation, which is obviously transformed into a drastic change of the torsional angles within the rest of the ring, *i.e.* the inherently chiral

chromophore. Again, the CD results characteristic for the chromophore and the NMR data characteristic for the non-absorbing part of the macrocycle<sup>9</sup> supplement each other nicely.

From molecular models it can be derived that acetylation of the C(7)-OH group of **2** to give **4** will not influence the ring conformation, and indeed this is reflected in its CD spectrum which is very similar to those of ketone **1** and alcohol **2** (Figure 2). By the same token the acetyl group of **5** does neither release nor enlarge steric strain, and the CD spectrum indicates this clearly, since it is very similar to that of the free alcohol **3**. Noticeably smaller Cotton effects of different shapes are, however, observed in the CD spectra of **3** and **5**, which indicates that their conformation differ from those of **2** and **4**. This was then confirmed by comparing the temperature dependence of the CD spectra of **1** and **6** (Figure 3, left and right).

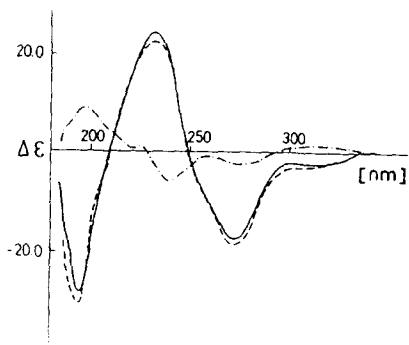


Figure 1. CD spectra of **1** (---), **2** (—), and **3** (- - -) in acetonitrile

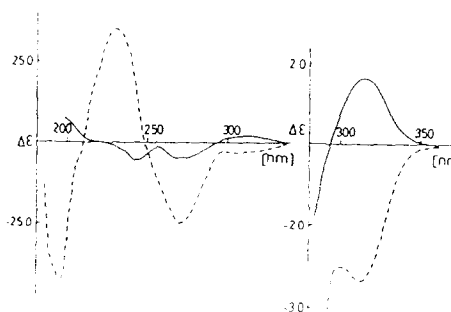


Figure 2. CD spectra of **4** (---), and **5** (—), in acetonitrile

Whereas for the first mentioned compound the strong negative CD band at 270 nm does not change in the temperature interval from +20° to -140°C neither in the position nor in intensity, in the latter this negative band disappears by cooling, whereas the first, positive band at ca. 315 nm gains more than double in intensity.

#### The CD spectra of $\alpha,\beta$ -isomers with Z-configuration

To our greatest surprise the CD spectrum of the Z- ketone **6** is also very similar in shape and magnitude to that of the isomeric ketone **1**. This implies that the whole chromophore must adopt this same absolute conformation in both stereoisomers (Figure 4). From the molecular models one can see that this same conformation with practically identical torsional angles can be adopted for **6** even better than for the E-isomer **1**. As also read off such models the surrounding of the keto group is not anymore so severely shielded on one side, and one can predict from this, that now both alcohols **7** and **8** should be able to adopt the same ring conformation. Again this is nicely proved by their CD spectra, although they differ in magnitude. The Cotton effects have identical signs, and even their relative magnitudes within each CD curve are quite similar, and similar to those of ketone **1**.

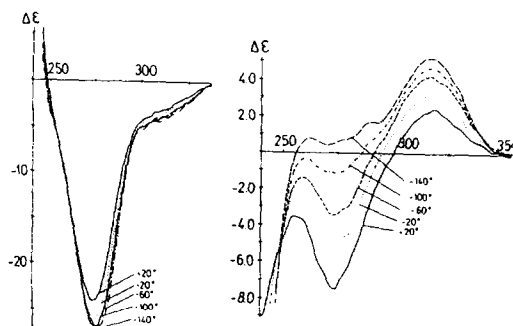


Figure 3. Temperature dependent CD spectra between 250-350 nm of **1** (left), and **6** (right), in EPA (ether-petrolether-acetonitrile 5:5:2)

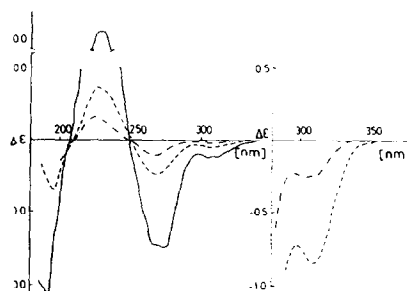


Figure 4. CD spectra of **6** (—), **7** (---) and **8** (-.-.-), in acetonitrile

Comparing the *E,Z*-pairs **1,6** (full lines in the Figures 1 and 4, *resp.*), **2,7** (broken lines), and **3,8** (dash-dot lines), one can notice similar shape and magnitude for the first pair of isomers, similar shape but significantly lower (*ca.* 60%) intensity for the second, and quite different shape of relative low intensity CD bands for the third. Some indications about conjugative interactions within the chiral chromophore offer the UV spectra of a few *E,Z*-pairs, Figure 5.

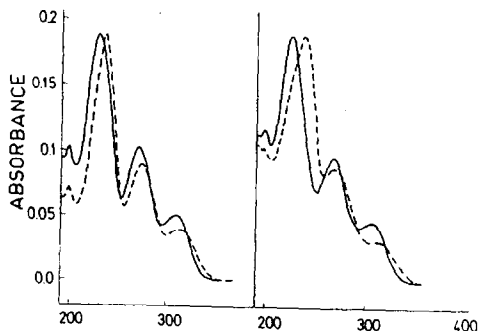


Figure 5. UV spectra of *E,Z*-zearalenones (**1,6**), and *E,Z*- $\alpha$ -zearalenols (**2,7**)

First, it was interesting to observe the regularity in the UV spectra of two *E,Z*-pairs. *Z*-isomers exhibit somewhat stronger first and second bands at *ca.* 310 nm and 270 nm, *resp.*, than the *E*-isomers. In some cases their maxima were also *ca.* 5-6 nm hypsochromically shifted. The third, strongest short-wave maximum was regularly hypsochromically shifted by *ca.* 6-10 nm. Interestingly, the UV spectrum of the C(11)-C(12) saturated compound **9** also exhibits hypsochromically shifted bands at 218, 263 and 302 nm, *resp.* The torsional angle of the C(11)-C(12)-C(12a)-C(1a) subunit for the solid-state structure of the 7-O-acetyl derivative of **9** was determined as  $-93^\circ$ , deviating for *ca.* 30-40° from those found for the *E*-isomers **1,2** and the **8**-

hydroxy congener of **1**, *i.e.*  $-111^\circ$ ,  $-119^\circ$ , and  $-134^\circ$ , *resp.* In the solid state structure of **1,2**, the  $7\alpha$ -O-acetyl derivative of **10**, and of the  $5\beta$ -hydroxy derivative of **1**, the torsional angle around the bond C(12a)-C(1a)-C(1)=O(1) deviates from planarity by  $4^\circ$  ( $\theta = -176^\circ$ ),  $1^\circ$  ( $\theta = -179^\circ$ ),  $18^\circ$  ( $\theta = -162^\circ$ ), and  $2^\circ$  ( $\theta = -178^\circ$ ), *resp.* These data indicate that similar position and intensity of Cotton effects of the two *E*-isomers **1** and **2** reflect similar (small) deviation from coplanarity (see Fig. 6. for illustration). To the same group belongs the  $5\beta$ -hydroxy derivative of **1**, whereas the larger deviation from coplanarity in the  $\alpha$ -O-acetyl derivative of **10** causes much weaker Cotton effects.

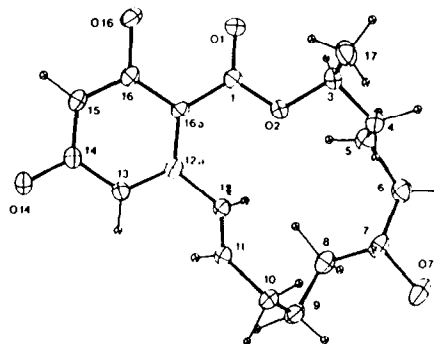


Fig. 6. ORTEP drawing of *E*- $\alpha$ -zearealenol (**2**), according to ref. 6.

It is also interesting that the UV spectra of **1** and of its C(11)-C(12) saturated congener **9** differ in the sense that the maxima for the saturated compound are hypsochromically shifted as compared to **1**, *i.e.* by 17 nm (from 234 to 217 nm), 9 nm (from 273 to 264 nm), and by 12 nm (from 315 to 303 nm), *resp.* Thus, the effect of the change of the torsional angles of the C(12a)-C(1a)-C(1)=O(1) and C(11)-C(12)-C(12a)-C(1a) subunits is more pronounced in the CD than in the UV spectra, as expected. These CD spectra reveal that the absence of conjugation in the compounds **9-11** rises the Cotton effects at *ca.* 200 nm, at 230 nm, at 260-270 nm, and at 300-307 nm, which are 4-5 times weaker than those of the corresponding unsaturated congeners, *i.e.* **9** vs. **1-6**, and **10** vs. **2**.

It seems that the main influence on the CD is caused by the deviation from coplanarity of the C(12a)-C(1a)-C(1)=O(1) moiety, since the C(11)-C(12)-C(12a)-C(1a) unit deviates much more from coplanarity in both the saturated and unsaturated congeners, irrespective of the sense of chirality at C(7). This small deviation from coplanarity can be caused either by the configuration at this chiral center C(7), or by the saturation of the C(11)-C(12) bond. No X-ray data for the *Z*-isomers are available, and therefore also not for this torsional angle C(12a)-C(1a)-C(1)=O(1). To explain the experimental CD data one has to assume a larger deviation from coplanarity for the alcohols **7** and **8**, but not for ketone **6**, however.

## CONCLUSIONS

Based on the sign of the first two Cotton effects, both negative at 310-315 nm, and at 270 nm, and the third, strongly positive one at 225-230 nm, in **1,2,4,6-8**, it can be concluded that all these molecules possess very similar conformations, characterized by a strongly negative torsional

angle C(11)-C(12)-C(12a)-C(1a). The absolute conformation in solution of the  $\beta$ -isomers **3**, **5**, and **8** seems not to be so well defined. The first, positive CD band at ca. 310-315 nm for **3** and **5**, and the very small negative one for **8**, along with the generally much lower intensities of all CD bands of these  $7\beta$ -isomers as compared to the  $7\alpha$ -isomers and to the ketones, indicate either the presence of several energetically similar conformations, or one rather different from that observed for the  $7\alpha$ -isomers and ketones. On the basis of the different temperature dependence of the spectra of **1** and **6** the first possibility seems more plausible.

## EXPERIMENTAL

Compounds **1-5** were prepared as described before<sup>8</sup>. The *Z*-isomers **6-8** were obtained from the corresponding *E*-isomers by irradiation with a Hg-high pressure UV lamp (125 W), under nitrogen stream through a MeOH solution, according to the described method<sup>7</sup>.

CD spectra were obtained for 1-2 mM solutions in acetonitrile, on a Dichrograph Mark III (ISA-Jobin-Yvon) connected on-line to a PC. Noise was eliminated by curve-smoothing according to the Golay-Savitzky algorithm (best parabola of degree 3 fitted to 25 consecutive points)<sup>10</sup>.

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## REFERENCES AND NOTES

1. F. G. Lu, J. Rendel (Editors), "*Anabolic Agents in Animal Production*", FAO/WHO Symposium, Rome, March, 1975.
2. R. G. Brown, in "*Anabolic Agents in Animal Production*", E. Meissonier, Editor, Symposium held at OIA, Paris, 15-17 February, 1983, pp. 155-188.
3. IMC Chemical Group, US Pat. 4,052,414 (1977).
4. C. J. Mirocha, S.V. Pathre, J. Behrens, B. Schauerhamer, *Appl. Environ. Microbiol.* 1978, **35**, 986.
5. I. F. Taylor, W.H. Watson, *Acta Crystallogr. Section B*, 1976, **32**, 710.
6. W. H. Watson, V. Zabel, C.J. Mirocha, S.V. Pathre, *Acta Crystallogr. Section B*, 1982, **38**, 1037.
7. C.A. Peters, *J. Med. Chem.* 1972, **15**, 867.
8. G. Snatzke, C. Angeli, E. Decorte, F. Moimas, B. Kojčić-Prodić, Z. Ružić-Toroš, V. Šunjić, *Helv. Chim. Acta*, 1986, **69**, 734.
9. W. B. Smith, W.H. Watson, *Magn. Res. Chem.* 1987, **25**, 975
10. Corrected data given in D. Ziessow, *On-line Rechner in der Chemie*, p. 345, Walter de Gruyter, Berlin, 1973.