79. Preparation *via* Diastereoselective Hydrogenation, Absolute Conformation and Configuration of Exogeneous Anabolic Zeranol ((3*S*,7*R*)-3,4,5,6,7,8,9,10,11,12-Decahydro-7,14,16-trihydroxy-3-methyl-1*H*-2-benzoxacyclotetradecin-1-one)

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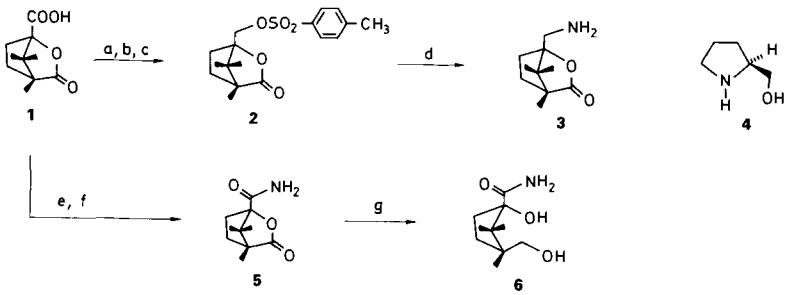
Hydrogenation of the ketone group in di-*O*-benzylderivative (**8**) of the known macrocyclic lactone zeralenone (**7**) using a novel chiral borane complex **3**·BH_3, prepared *in situ*, proceeded at lower temperatures with moderate diastereoselectivity (~ 40%, d.e. at −60°). Unsaturated diastereomers **9** and **10** were separated, and **9** converted into zeranol (**11**), a known anabolic agent. Restricted conformational mobility at lower temperatures is assumed for the intermediate **8** on the basis of the temperature-dependent CD spectra of its acetyl congeners **18** and **19**. X-Ray structure analysis of 7-*O*-acetylderivative (**13**) of **11** revealed the (*R*)-configuration at C(7). Two crystallographically independent H_2O molecules are involved in the H-bonds, one of them (O(21)) rises the helices of the molecules of **13** along $\vec{b}$. Small positive torsional angle [C(16)–]C(161)–C(1) [= O] (+19.3°), *transoid* (*E*) conformation of the lactone group, and nearly achiral arrangement of the C(11)–C(12) bond (torsional angle [C(11)–]C(12)–C(121)[C(161)] is −93°) are the main conformational features that differentiate the macrocyclic RAL (resorcinic-acid lactone) derivatives from the 6-membered lactone derivative **20**, studied earlier by CD. Consequently, the rules developed for the CD effects within conjugation band (around 270 nm), and n→π* band (around 255 nm) of the latter compound, cannot be applied the macrocyclic lactones.

1. Introduction. – Zeranol (**11**, see *Scheme 2*) is an exogeneous anabolic that increases growth performance in ruminants [1] [2]. The common fungus *Giberella zeae* produces a macrolide ketone called zeralenone (**7**), that, on hydrogenation of the C=C bond and ketone C=O group gives diastereoisomeric mixture of **11** and its 'low-melting' diastereoisomer **12** [3–5]. They were separated by the conventional methods [3] [6], affording pure **11**, for which a high growth-promoting activity with low estrogenicity was repeatedly established. Absolute configuration at biosynthetically created chiral centre C(3) was determined [7] as *S*, while absolute configuration of the second chiral centre, at C(7), seems not to be published. In [8], however, wrong configurations at C(7) are ascribed to the 'high-melting' and 'low-melting' diastereoisomer, based on the cited unpublished results.

Here, we describe diastereoselective hydrogenation of **8**, determination of absolute configuration of **13** by X-ray structure analysis, as well as the chiroptical properties of this class of macrolide compounds.

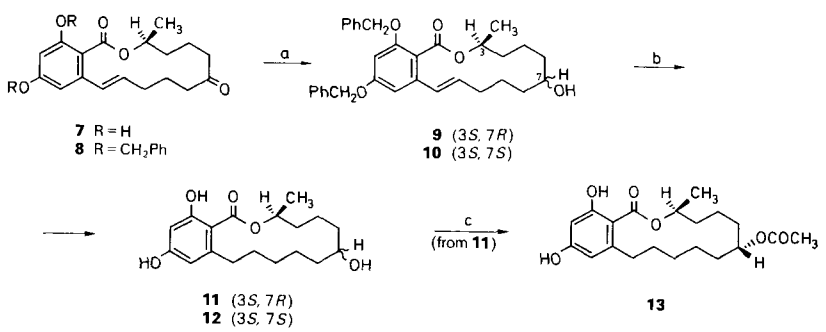
2. Results and Discussion. – 2.1. *Synthesis.* (+)-Zeralenone (**7**) was benzylated as described in [9], and resulting **8** was hydrogenated with borane complexes of the chiral ligands **3** and **4**, prepared *in situ*. Chiral amine **3** was prepared by ammonolysis of tosylate **2** [10], performed at elevated temperature and pressure *(Scheme 1)*. The alternative route *via* camphanic amide **5** [11] gave on reduction with excess of $LiAlH_4$ the diole **6** as the main product, in contrast to our earlier finding [10] that equimolar amount of $LiAlH_4$ reduces selectively camphanic esters leaving lactone ring unchanged. Hydrogenation of **8** with **3**·BH_3 was attempted under various conditions *(Exper. Part)* only moderate stereoselectivity (→**9**/**10**) was achieved at low temperatures. With **4**·BH_3, inverse but still

Scheme 1



a) EtOH/HCl; b) $LiAlH_4$/THF; c) TsCl/Py; d) EtOH/NH_3/Δ; e) $SOCl_2$/Δ; f) NH_3/C_6H_6; g) $LiAlH_4$/THF

Scheme 2



a) 3/B_2H_6/toluene; b) *Ra*-Ni/H_2/EtOH; c) $Ac_2O/H^+/\Delta$

low diastereoselectivity was obtained. The ratio **9**/**10** was determined quantitatively by the analytical HPLC. After their separation on preparative scale and subsequent hydrogenation of the C=C bond with concomitant hydrogenolysis of the protecting groups, pure **11** and **12** were obtained, possessing identical chiroptical properties as the samples obtained by the conventional separation methods [3] [6] *(Scheme 2)*.

2.2. *Crystal and Molecular Structure of* **13**. An attempt to solve the crystal structure of **11** itself failed; the twin crystals obtained from MeOH/H_2O were of poor quality. Therefore, its 7-*O*-acetylderivative **13** was prepared, and crystallized from MeOH/H_2O

Table 1. *Interatomic Distances* (Å) *and Angles* (°) *for Non-H-Atoms*

C(1)–O(1)	1.232(4)	O(2)–C(3)–C(4)	105.1(3)
C(1)–O(2)	1.330(4)	C(31)–C(3)–C(4)	112.7(3)
C(1)–C(161)	1.468(4)	C(3)–C(4)–C(5)	115.1(3)
C(3)–O(2)	1.474(4)	C(4)–C(5)–C(6)	112.9(3)
C(3)–C(31)	1.504(5)	C(5)–C(6)–C(7)	113.3(3)
C(3)–C(4)	1.508(4)	C(6)–C(7)–O(71)	108.8(3)
C(4)–C(5)	1.524(5)	C(6)–C(7)–C(8)	114.7(3)
C(5)–C(6)	1.534(4)	C(6)–C(7)–O(71)	108.8(3)
C(6)–C(7)	1.506(6)	C(8)–C(7)–O(71)	106.7(3)
C(7)–C(8)	1.510(5)	O(71)–C(71)–O(72)	122.9(3)
C(7)–O(71)	1.461(4)	O(71)–C(71)–C(72)	113.4(4)
C(71)–O(71)	1.305(3)	O(72)–C(71)–C(72)	123.5(4)
C(71)–O(72)	1.177(6)	C(7)–O(71)–C(71)	119.5(3)
C(71)–C(72)	1.494(4)	C(7)–C(8)–C(9)	115.1(3)
C(8)–C(9)	1.511(6)	C(8)–C(9)–C(10)	114.5(3)
C(9)–C(10)	1.512(6)	C(9)–C(10)–C(11)	115.1(4)
C(10)–C(11)	1.512(4)	C(10)–C(11)–C(12)	114.0(3)
C(11)–C(12)	1.519(5)	C(11)–C(12)–C(121)	112.8(3)
C(12)–C(121)	1.516(4)	C(12)–C(121)–C(13)	116.2(3)
C(121)–C(161)	1.417(5)	C(12)–C(121)–C(161)	124.6(3)
C(121)–C(13)	1.377(4)	C(13)–C(121)–C(161)	119.2(3)
C(13)–C(14)	1.387(4)	C(121)–C(13)–C(14)	121.8(3)
C(14)–O(14)	1.355(5)	C(13)–C(14)–C(15)	120.0(3)
C(14)–C(15)	1.377(5)	C(13)–C(14)–O(14)	116.8(3)
C(15)–C(16)	1.391(5)	O(14)–C(14)–C(15)	123.1(3)
C(16)–O(16)	1.355(4)	C(14)–C(15)–C(16)	119.8(3)
C(16)–C(161)	1.416(4)	C(15)–C(16)–O(16)	116.7(3)
O(1)–C(1)–C(161)	123.1(3)	C(15)–C(16)–C(161)	120.7(3)
O(1)–C(1)–O(2)	121.0(2)	O(16)–C(16)–C(161)	122.6(3)
O(2)–C(1)–C(161)	115.9(2)	C(1)–C(161)–C(121)	125.6(3)
C(1)–O(2)–C(3)	117.7(2)	C(1)–C(161)–C(16)	116.0(3)
O(2)–C(3)–C(31)	110.4(3)	C(16)–C(161)–C(121)	118.3(3)

4:1 affording acceptable crystallographic sample. Its interatomic distances and angles are listed in *Table 1*.

The torsional angles describing the conformation of the macrocyclic ring and orientations of the ring substituents are given in *Table 2*. Molecular conformation and atom numbering are shown in *Fig. 1*. *Fig. 2* illustrates the molecular packing *via* H-bonds.

Table 2. *Torsional Angles* (°)

O(1)–C(1)–O(2)–C(3)	3.3(5)	C(6)–C(7)–O(71)–C(71)	102.3(4)
C(161)–C(1)–O(2)–C(3)	–178.6(3)	C(7)–O(71)–C(71)–C(72)	179.5(4)
C(1)–O(2)–C(3)–C(4)	–164.1(3)	O(71)–C(7)–C(8)–C(9)	89.1(3)
C(1)–O(2)–C(3)–C(31)	74.1(4)	C(7)–C(8)–C(9)–C(10)	66.0(4)
O(2)–C(3)–C(4)–C(5)	68.2(4)	C(8)–C(9)–C(10)–C(11)	64.5(5)
C(3)–C(4)–C(5)–C(6)	–175.9(3)	C(9)–C(10)–C(11)–C(12)	–179.2(3)
C(4)–C(5)–C(6)–C(7)	66.4(4)	C(10)–C(11)–C(12)–C(121)	–179.9(3)
C(5)–C(6)–C(7)–C(8)	72.4(4)	C(11)–C(12)–C(121)–C(161)	–93.1(4)
C(5)–C(6)–C(7)–O(71)	–168.1(3)	C(12)–C(121)–C(161)–C(1)	0.3(5)
C(6)–C(7)–C(8)–C(9)	–150.3(3)		

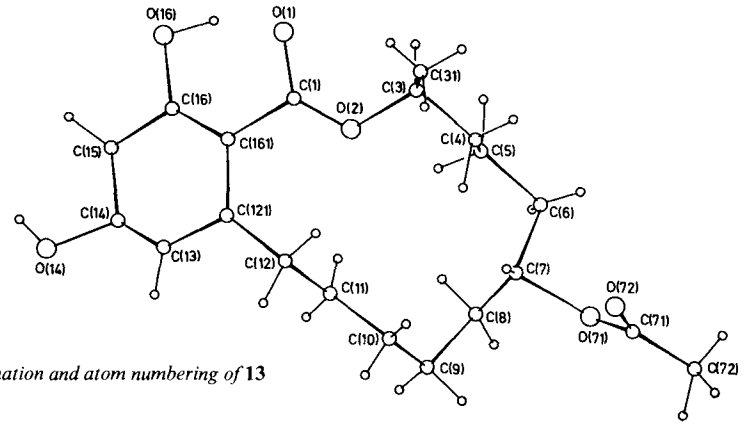


Fig. 1. *Molecular conformation and atom numbering of* **13**

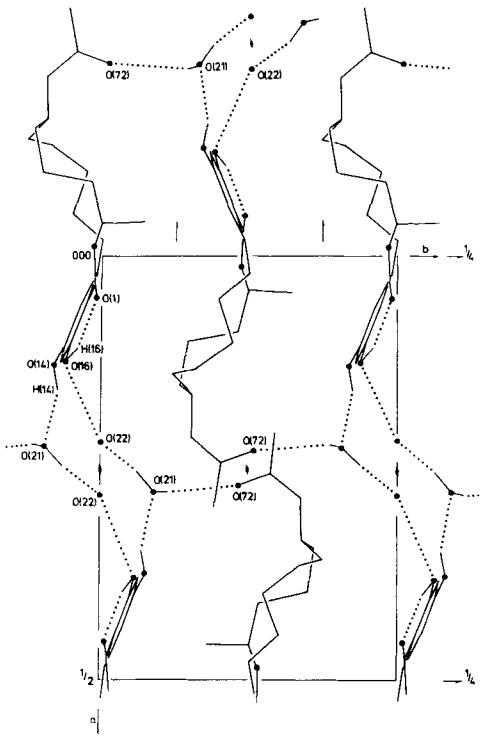


Fig. 2. *Molecular packing viewed along* c, *illustrating H-bond network*

2.3. *Molecular Geometry.* The molecular skeleton involves a 14-membered lactone ring *ortho*-fused to a 1,3-dihydroxybenzene moiety. Previously described 7-hydroxyzeralenol/MeOH solvate [12] and 5-hydroxyzeralenol·H_2O [13] exhibit similar values of bond lengths, bond and torsional angles. The mean values of endocyclic bond parameters of C(sp^3) are: for bond distances 1.5415(5) Å and bond angles 114.2(3)°. Differences in the C–O bond distances involving C(sp^3) are within 3σ; the same applies to those involving C(sp^2). The values of torsional angles *(Table 2)* and planarity of molecular segments

illustrate the conformation of the macrocyclic ring. There are three planar segments in the molecule. The largest one involves the phenyl ring (C(121)→C(161)), O(14), C(1), and C(12) with deviations from the least-squares plane 0.007(6)–0.033(6) Å. Coplanarity of O(16), O(1), and O(2) expected by hybridization is not confirmed. The atoms O(1) (0.277(7) Å), O(16) (0.111(7) Å), and O(2) (–0.436(6) Å) deviate from planarity. This effect might be explained by intramolecular H-bond O(16)–H···O(1) (2.521(4) Å). The two small planar fragments are those involving C(3), C(4), C(5), C(6) with deviations from planarity (0.02(6)–0.03(6) Å) and C(7), O(71), C(71), O(72), C(72) (0.00(5)–0.02(5) Å). The absolute configuration at two chiral centres is (3*S*, 7*R*) and signs of torsional angles are in accord.

2.4. *Molecular Packing.* Two crystallographically independent H_2O molecules are involved in H-bonds. The H_2O molecule O(21) is H-bonded to the CO group of the AcO residue O(21)–H···O(72) (2.774(6) Å) and to one of the OH group of resorcine moiety O(14)–H···O(21), (2.669(4) Å) forming helices along $\vec{b}$ *(Fig. 2)*. The O(21) H_2O molecules acts as donor to another one, O(22) (2.729(8) Å). The entire function of O(22) in the system of H-bonds is somewhat uncertain, because no reliable H positions could be secured. A weak interaction O(22)···O(16) (3.003(7) Å) along $\vec{c}$ was observed. The same type of interaction is found in the crystal structure of 5-hydroxyzearalenol·H_2O (3.137(9) Å) [13] [14]. According to the H-bond scheme *(Table 3)* is obvious that the O(21) H_2O molecule is more tightly bonded in the crystal lattice than the O(22) H_2O molecule. Thermogravimetric measurements have given evidence about that; weight loss corresponding to one H_2O molecule was below 343 K.

Table 3. *H-Bonds*

D–H···A	D···A (Å)	D–H (Å)	H···A (Å)	∢ D–H···A (°)	Symmetry operation on A
O(14)–H(14)···O(21)	2.669(4)	0.82(5)	1.88(6)	160(5)	$-x, \frac{1}{2}+y, \frac{1}{2}-z$
O(16)–H(16)···O(1)	2.521(4)	0.98(5)	1.61(5)	153(4)	$x, y, z,$
O(21)–H(211)···O(72)	2.774(6)	1.10	1.70	164	$x, y-1, z,$
O(21)–H(212)···O(22)	2.729(8)	1.02	1.73	167	$\frac{1}{2}-x-1, 1-y, \frac{1}{2}+z-1$
O(22)···O(16)	3.003(7)	–	–		$-x, \frac{1}{2}+y-1, \frac{1}{2}-z+1$

The conformation of the molecule is stabilized by an intramolecular H-bond. The *ortho*-substituents with donor/acceptor sites enable the formation of intramolecular H-bond. This type of interaction affecting lactone group and one of the OH groups of the resorcine moiety was observed in the compound **13** and also in the 5-hydroxy- (2.518(8) Å [13]) and 7-hydroxyzeralenol (2.502(3) Å [12]) derivatives.

2.5. *CD Study.* The chromophore of **11** and its derivatives is that of substituted resorcinic acid; it is inherently chiral (axis of chirality along Ph-COOR bond) because of steric interference with the rest of the lactone ring; it is substituted by one alkyl chain which forms part of the lactone ring. This chromophore system is thus identical with that of (–)-6-hydroxymellein (**20**) [15]. X-Ray diffraction measurements, described above for **13**, proved the same (*S*) configuration at C(3) of **11**, as in two other related natural products [12] [13], while the configuration at C(7) turned out to be *R*. From the same measurements the torsional angle [C(16)–]C(161)–C(1) [= O] was determined as +19.3°;

its sign is thus opposite to the sign of corresponding torsional angle in **20** (estimated from *Dreiding* models as *ca.* −15°).

Recently, we have found [15] that the sign of the n→π* *Cotton* effect of the lactone chromophore is negative, *i.e.* as the sign of the mentioned torsional angle, whereas the signs of the π→π* *Cotton* effects depend also on the substitution pattern of the aromatic ring. In the meantime, we have proved this also with the help of synthetic mono- and

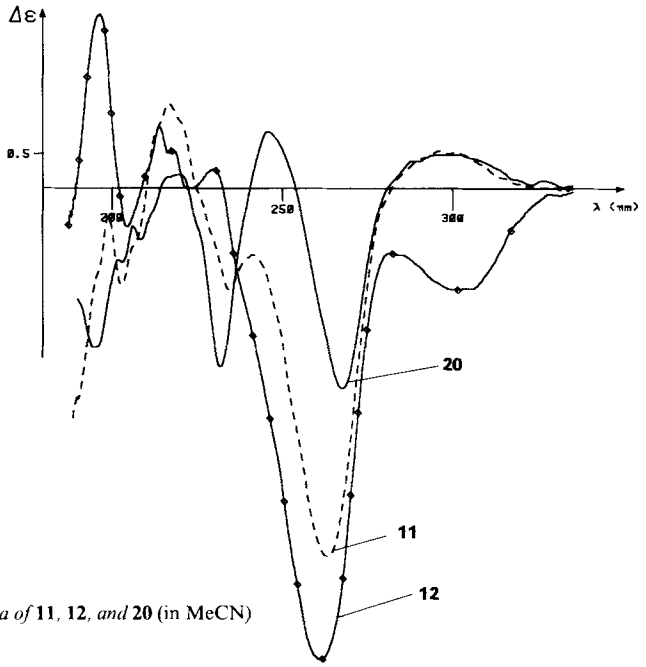
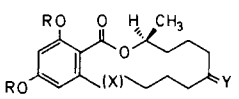
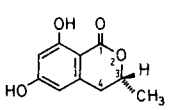


Fig. 3. *CD Spectra of* **11**, **12**, *and* **20** (in MeCN)



	R	X	Y (config.)
13	H	CH_2CH_2	H, Ac (*R*)
14	H	CH_2CH_2	H, Ac (*S*)
15	Ac	CH_2CH_2	H, Ac (*R*)
16	Ac	CH_2CH_2	H, Ac (*S*)
17	H	CH_2CH_2	=O
18	Ac	CH_2CH_2	=O
19	Ac	CH=CH	=O



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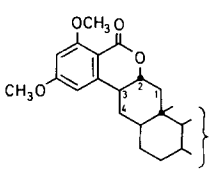

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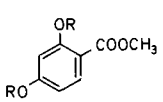

22 R = H
23 R = Ac

Table 4. *CD and UV Data for* **7**, **11**–**19**, **22**, *and* **23**

Compound	CD [nm] ($\Delta\varepsilon$)/Solvent: CH_3CN	UV [nm] (log ε)/Solvent
7	22.9 (+17.90), 272.6 (−17.93), 307.0 sh (−2.63)	234.0 (4.40), 273.0 (4.04), 314.5 (3.69)/MeOH
11	196.8 (+3.53), 197.4 (+3.56), 207.4 (+0.77), 212.0 (+1.14), 229.2 (+0.64), 261.2 (−6.70), 301.0 (−1.62)	218.0 (4.47), 263.0 (4.10), 302.5 (3.76)/MeOH
12	203.0 (−1.43), 216.6 (+1.23), 234.6 (−1.49), 163.4 (−5.42), 295.6 (+0.54), 300.4 (+0.52)	214.5 (4.32), 262.0 (3.90), 237.0 (3.78)/MeOH
13	191.2 (+7.37), 196.2 (+7.30), 216.0 (+3.13), 224.4 (+3.14), 230.2 (+3.34), 261.4 (−5.25), 301.9 (−1.42)	263.5 (4.49), 304.0 (4.09)/THF
14	204.4 (−0.72), 216.2 (+1.66), 233.6 (−1.09), 263.6 (−4.70), 292.8 (+0.79), 296.2 (+0.78), 300.8 (+0.77)	264.0 (4.13), 304.0 (3.75)/THF
15	197.6 (−11.57), 239.6 (+6.76), 278.2 (+0.22), 283.0 (+0.20), 287.5 (+0.22)	244.5 (3.40)/$CHCl_3$
16	197.5 (−8.16), 238.4 (+7.06), 277.2 (−0.53), 281.2 (−0.52), 285.8 (−0.64), 290.0 (−0.62)	248.5 (3.25)/$CHCl_3$
17	194.8 (+6.16), 230.6 (+1.40), 260.0 (−7.60), 299.2 (−4.60)	217.5 (4.38), 264.0 (4.11), 302.5 (3.72)/MeOH
18	241.0 (+6.02), 290.8 (+1.00)	205.5 (4.46)/MeOH
19	188.7 (+11.50), 206.0 (−1.73), 210.2 (−2.54), 212.7 (−2.36), 220.4 (−1.50), 223.1 (−1.32)	218.0 (4.42), 251.5 (4.19)/MeOH
22	225.0 (−1.26), 234.2 (−0.60), 263.0 (−3.08), 267.0 (−3.09), 295.5 (+0.01), 319.8 (−0.02)	259.0 (4.04), 295.0 (3.74)/EtOH
23		233.0 (4.14), 270 (sh; 3.31), 280 (sh; 3.23)/EtOH

disubstituted isochromanones, in which this moiety is attached to the steroid skeleton [16]. We expected, therefore, positive signs for those n→π* *Cotton* effects for **11** and **20**, found them, however, to be both negative *(Fig. 3)*.

At largest wavelengths the α-band- (B_{2u} for benzene), *Cotton* effect is found around 300 nm, and it is positive for **20**, but negative for **11**. Its position coincides with that of the corresponding UV band *(Table 4)*.

The 'conjugation band' (B_{1u} for benzene) appears around 270 nm in the CD and the UV spectra, and both *Cotton* effects are negative for **11** and **20**. The n→π* band *Cotton* effect has been assigned [15] to a shoulder in the CD spectrum of **20** around 255 nm. It is negative for **20** and also negative for **11**, although it cannot be very distinctly seen. The acetate **13** gives a CD spectrum which is very similar to that of alcohol **11** *(Table 4)*.

Under the reasonable assumption that the conformation of the lactone ring of **13**, which is found in the crystal, is also the preferred one in the solution of **11** and **13**, CD curves of enantiomorphic character to those of **20** are expected. As possible reasons for the observed opposite signs within the second and third *Cotton* effect, two conformational differences seem to be responsible. Firstly, the configuration of the lactone moiety of **20** must be *E ('transoid')*, whereas in **13** it is found to be *Z ('cisoid')*. All regularities which hitherto have been observed for lactones were proved only for the *'cisoid'* case, and we know, therefore, not whether they also can be applied to *'transoid'* lactones. Secondly, the σ-bond C(11)–C(12) is positioned in a plane nearly orthogonal to the benzene chromophor in **13** (torsional angle [C(11)–]C(12)–C(121)[C(161)] is −93°), *i.e.* in a nearly achiral arrangement with respect to the chromophore, whereas the corresponding torsional angle of **20** is *ca.* +25° (as estimated from *Dreiding* models). That this latter fact is

of importance follows *e.g.* from a comparison of the CD spectra of **20** and **21**, whose hetero-rings must have identical conformations. The CD within the conjugation and the n→π* bond, as well as the next two *Cotton* effects (247 nm positive, negative at shorter wavelength) for these both compounds have identical signs and similar shapes, but they have opposite signs within the first absorption band (α-band) [16]. The chiral perturbations of the chromophore by the σ-bonds C(2)–C(3) and C(3)–C(4) (usual numbering for ring A of steroid skeleton) nearly compensate each other in **21**, whereas in **20** no such compensation of the chirally arranged C(3)–C(4) bond is present.

The CD of the diastereoisomer **12** of zeranol and its acetate **14** are also very similar to each other *(Table 4)*. For both diastereoisomers **11** and **12**, the CD within the conjugation band and the n→π* band (again only seen as a shoulder) have the same signs *(Fig. 3)*. Whether the *Cotton* effects at wavelengths smaller than 250 nm have opposite signs (and identical band positions) or same signs (and then slightly different positions, which might be caused merely by addition of two bands of quite different magnitudes) cannot be decided from the inspection of the CD curves alone. Within the α-band, both compounds show *Cotton* effects of the opposite signs, and this feature can be interpreted in the following way. In **13** (and obviously also in **11** because of the identical CD curves), the C(7)-OR group adopts a quasi-equatorial conformation. If a similar situation holds also for the C(7) epimers **12** and **14**, then the lactone ring has to adopt a completely different overall conformation, the torsional angle [C(16)–]C(161)–C(1) [= O] should, however, remain positive. Since the absolute configuration at C(3) in both pairs remains unchanged, that half of the ring (C(1) to C(6)) will approximately retain its overall shape,

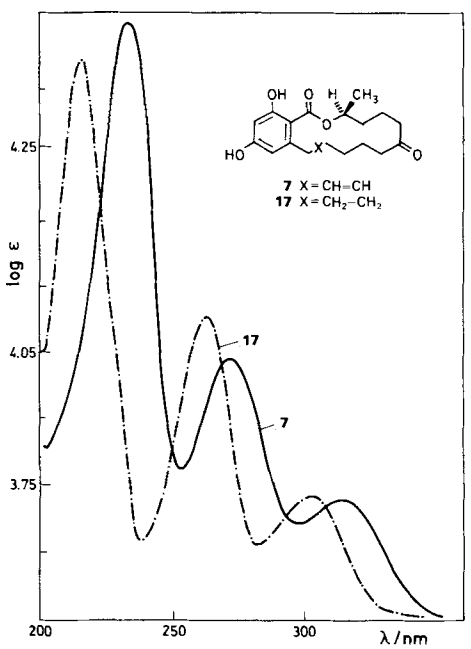

Fig. 4. *UV Spectra of* **7** *and* **17** (in EtOH)

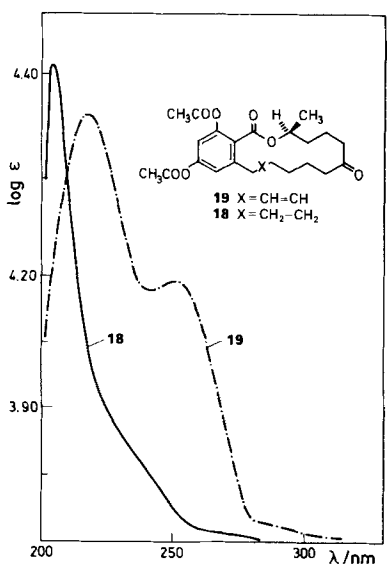

Fig. 5. *UV Spectra of* **18** *and* **19** (in EtOH)

whereas the main change should take part in the second half of the large ring. If, by this change of conformation the absolute value of the torsional angle [C(11)–]C(12)–C(121)–[C(161)] deviates then distinctly from 90°, its main influence should, according to the discussion above, be seen within the α-band *Cotton* effect, which is the case.

The CD spectrum of ketone **17** resembles very much to that of zeranol **11** with the exception that the *Cotton* effect around 300 nm is much stronger negative. This indicates that the helicity around the C(1)–C(161) bond is the same in both molecules and that the *Cotton* effect of the C=O n→π* bond is negative ($\Delta\varepsilon$ *ca.* −3 to −5). Such a large value indicates a rather conformational rigidity of the lactone ring, and it is reminescent of the CD of twisted cycloalkanones [17].

On acetylation of both phenolic OH, the UV and CD spectra change drastically (*Figs. 4* and *5*, and *Table 4*). The α-band becomes visible only as a shoulder and is blue-shifted by *ca.* 20–25 nm. The conjugation band is also hypsochromically shifted from *ca.* 262 nm to *ca.* 245 nm. These shifts of the bands turned out to be a general feature for 2,4-dihydroxy-benzoates, as in the spectra for methyl resorcinate (**22**) and its diacetate **23** (*Table 4*).

The CD curves of **15** and **16** are very similar, showing only one strong positive *Cotton* effect around 240 nm and the beginning of another negative one at shorter wavelengths. The first mentioned one corresponds to the conjugation band, and if the lactone n→π* *Cotton* effect is in its usual position, then it is also positive (shoulder of the large *Cotton* effect), but no *Cotton* effect could be detected in the range of the α-band, what means that it is *ca.* two orders of magnitude smaller than for the free phenols **11** and **12**.

The diacetate **18** derived from **17** exhibits a CD spectrum in which the strong *Cotton* effect remains practically unchanged, but it shows the appearance of a new positive *Cotton* effect around 290 nm, which is then most probably the n→π* *Cotton* effect of the ketone (*Fig. 4*).

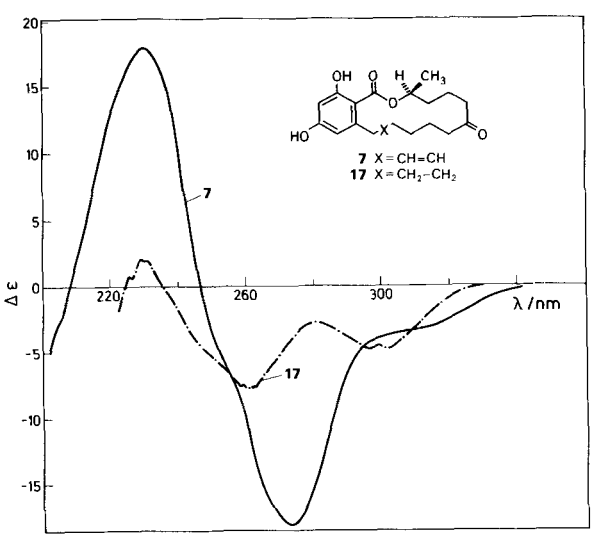

Fig. 6. *CD Spectra of* **7** *and* **17** (in MeCN)

The sign inversion of the conjugation-band *Cotton* effect by going from **17** *(Fig. 6)* to **18** (*Fig. 8*, curve at +20°) does not necessarely indicate a change of the inherent helicity of the chromophore system, since we know that the change of the substitution of the aromatic ring can sometimes influence the signs of the CD bands. The n→π* *Cotton* effect of the keto group should, however, not be influenced at all by the acetylation of the two phenolic OH groups. The positive sign proves thus a change of at least the near surrounding of the 7-carbonyl group of **18** by acetylation. This, in turn, can only be understood if also the torsional angle around the C(1)–C(161) bond is drastically changed by the replacement of OH by AcO. Also the strong blue shift of the conjugation band can best be explained, besides by the mesomeric effect, by a weaker coupling between the benzene ring and the COOR moiety caused by larger deviation from coplanarity.

A C(11)=C(12) bond in **7** changes of course the whole chromophore system discussed for saturated compounds, and all strong UV bands are shifted bathochromically as expected for the additional conjugation *(Fig. 4)*.

Three strong *Cotton* effects are shifted to larger wavelength, and their $\Delta\varepsilon$-values are relatively large. Neither the n→π* band *Cotton* effect of the ketone nor that of the lactone chromophore can be identified with certainty because of the overlap with the strong π→π* *Cotton* effects. Since both helicities around the C(1)–C(161) and the C(12)–C(121) bonds will strongly influence the individual *Cotton* effects, we cannot deduce the details of the conformation of the lactone ring from the CD *(Fig. 5)*. The large values prove, however, that at least one of these torsional angles should be in the range of 30–60° (absolute value). For two related compounds [12] [13] torsional angles [C(11)–]C(12)–C(121)–[C(161)] of −139° and −139.6°, respectively, have been found in the crystalline state, what means *ca.* 40° deviation from coplanarity for the C=C bond.

The COOR moiety is in these two cases nearly coplanar with the benzene ring, deviations from coplanarity amount to +1° and −5.4°, respectively [12] [13]. Unfortunately, no CD data have been published for these compounds.

Also here, the acetylation of the phenolic groups in **7** (affording **19**) changes drastically the UV and CD spectra *(Figs. 4* and *5)*. The strong UV conjugation band of **7** is shifted from 235 nm to 217 nm by acetylation, but is nearly as strong as in the diphenol. The 272-nm band is blue-shifted to *ca.* 252 nm and is even somewhat increased, whereas the 317-nm band ($\varepsilon \approx 6000$) has disappeared completely, or may perhaps be associated with the weak inflection around 285 nm ($\varepsilon \approx 1000$).

Since acetylation should not influence the surrounding of the C=O chromophore, a negative *Cotton* effect is still expected for **19**, as for **7**, we see, however, only a very small negative *Cotton* effect around 320 nm, *(Table 4)* and another positive one around 295 nm, which is also very small. If both belong to n→π* transition of the C=O, than this data could be explained by assuming that the AcO group at C(16) interfers sterically with the lactone moiety which will give rise to a change of the conformation of the large ring. It is not unusual that this *Cotton* effect is bisignated. It can, however, not be excluded that the positive CD band at around 295 nm corresponds to a π→π* transition of the aromatic system.

Since the *Cotton* effect around 270 nm of **7** *(Fig. 6)* coincides in position with the UV maximum *(Fig. 4)*, one would expect the same for the diacetate **19**; at the corresponding position one finds at most a shoulder. The CD band around 265 nm of **19** ($\Delta\varepsilon \approx -3$) could thus be associated with the lactone n→π* transition, since it is just in the expected

wavelength range. The helicity around the C(1)–C(161) bond, introduced by acetylation and discussed above, must than have the same sign as in the saturated analogs, where also a negative n→π* band *Cotton* effect was observed.

Within the conjugation band the g number ($g = \Delta\varepsilon/\varepsilon$) is so small that the corresponding *Cotton* effect cannot be measured with better accuracy. Below 200 nm the CD becomes than positive *(Table 4)*. The conclusions about the change of conformation of the lactone ring induced by acetylation, and those drown from the CD bands above 250 nm are mutually consistent.

To study the possibility of such conformational changes in more detail, we determined also the temperature dependence of the CD of **19** in Et_2O/light petroleum/MeCN 5:5:2, see *Fig. 7*.

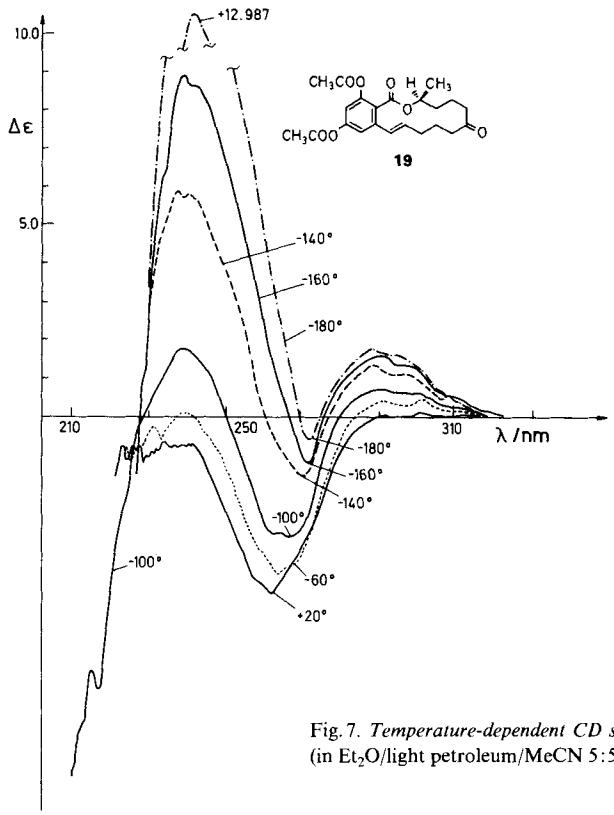

Fig. 7. *Temperature-dependent CD spectra of* **19** (in Et_2O/light petroleum/MeCN 5:5:2)

The CD curve at +20° resembles very much to that in MeCN. By lowering the temperature, the ketone n→π* *Cotton* effect is continuously rising to a positive value of *ca.* 1.5, at *ca.* 290 nm, and a very drastic change can be noticed between 280 nm and 220 nm. A very strong positive *Cotton* effect ($\Delta\varepsilon = +12.9$) is quickly developing, and the negative CD band around 256 nm nearly disappears at −180°. This latter change may be a mere consequence of the overlap of these two *Cotton* effects. Such anomalous strong changes of the CD with temperature can only be explained by an equilibrium of at least two conformers with relatively small difference in potential energy. Since both, the

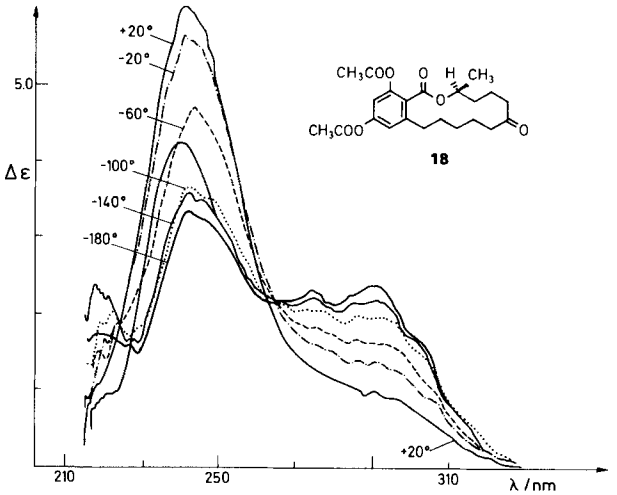

Fig. 8. *Temperature-dependent CD spectra of* **18** (in Et_2O/light petroleum, MeCN 5:5:2)

rotation around C(12)–C(121) as well as C(1)–C(161) bond could take place and will change the inherent chirality of the chromophore, we would like to refrain from the assigning definite conformations to those individual species.

Temperature-dependent CD spectra of **18** *(Fig. 8)* revealed the same behaviour of the ketone $n \rightarrow \pi^*$ *Cotton* effect at *ca.* 290 nm. Decreasing intensity of the second positive band at *ca.* 250 nm at lower temperatures cannot be interpreted unambiguously because of the complexity of the related chromophoric system.

G. S. thanks Mr. *U. Wagner* for the skilfull CD measurements, *Deutsche Forschungsgemeinschaft, Fonds der Chemie* und *Hoechst AG* for financial support, *B. K.-P.* thanks Prof. *A. F. Peerdeman*, Dept. of Structural Chemistry, University of Utrecht for the facilities placed at her disposal, and *A. J. M. Duisenberg* for data collection.

Experimental Part

General. The m.p. determined with a *Kofler* microheating stage *(Böetius)* are uncorrected. TLC was performed on aluminum plates with *Merck* silica gel *60* F_{254}, column chromatography was run over granular silica gel 0.05–0.2 mm *(Merck)*. Org. extracts were regularly dried over Na_2SO_4 and evaporated *in vacuo*. Optical rotations were measured on a *Perkin-Elmer 141*. UV: λ_{max} [nm] (log ε) *PYE Unicam SP 8-100* instrument. CD: a *Dickrograph Mark III* (ISA-*Jobin-Yvon*) connected on-line to a *PDP-8e*. Noise was eliminated by curve-smoothing according to the *Golay-Savitzky* [24] algorithm (best parabola of degree 3 filtered to 25 consecutive points). IR (for KBr pellets, in cm^{-1}): *Perkin Elmer M 297* spectrometer. ^{1}H-NMR: *Perkin Elmer R 12* and *Varian FX 90Q* instruments. Chemical shifts are reported in δ values relative to TMS as a standard.

X-Ray Data. The crystals of **13** for X-ray analysis were prepared from H_2O/MeOH 1:4 at r.t. Preliminary cell dimensions and the space group ($P2_12_12_1$) were determined from oscillation and *Weissenberg* photographs recorded with Cu$K\alpha$ radiation: final cell dimensions (a = 28.244(2), b = 9.503(1), c = 8.142(1) Å) were refined from diffractometer measurements using 16 reflexions. Intensities were collected on an *Enraf-Nonius CAD-4F* diffractometer in the $\omega/2\theta$ scan mode parameters A = 0.50, B = 0.15 in width A + Btanθ, horizontal (1.3 mm) and vertical (4.0 mm) apertures with Cu$K\alpha$ radiation at 293 K. Dimensions of crystal were 0.10 × 0.90 × 0.25 mm. 2071 independent reflexions $I \geq 2.5\,\sigma(I)$ in the range $2 < \theta < 70°$ were used in the calculations; 4 reference reflexions ($\bar{3}$ $\bar{1}$ $\bar{1}$, $\bar{3}$ 1 $\bar{1}$, 3 $\bar{1}$ $\bar{1}$, 3 1 1) showed short-term fluctuations less than 1% during 62 h of X-ray exposure time. *Lorentz*-polarization corrections were applied. The structure was solved by direct methods, MULTAN 80 [18]. A subsequent difference synthesis located the H-atoms except those of CH_3–C(7) group and one of two H_2O

molecules (O(22)). At C(7), they were introduced at calculated positions and treated as the rigid group [19]. The impossibility to locate the H-atoms of the O(22) H_2O molecule can be explained by its high thermal motion (U_{eq} = 18.2(3) Å^2). Full-matrix least-squares refinement, minimized $\Sigma w(|F_o| - |F_c|)^2$ with $w^{-1} = \sigma^2(F_o) + g F_o^2$(g = 0.001). A scale factor, atomic coordinates, and anisotropic thermal parameters were refined; atomic coordinates and overall isotropic thermal parameter of the H-atoms were refined. The absolute configuration at C(3) has been assigned in zeralenone [7] [20]. It was used as an internal standard, and the absolute configuration at the new chiral centre was determined; the absolute configuration of the molecule is (3*S*, 7*R*). The final R = 0.054, R_w = 0.064 for 2071 observed reflexions. The ratio of maximum least-squares shift to error on coordinates in the final refinement cycle was 0.553 (for z of C(16)). Residual electron density: $-0.1 < \Delta\rho < 0.1$ eÅ^{-3}. Scattering factors from *Cromer* and *Mann* [21] and (for H) *Stewart et al.* [22] were used. *Table 5* lists the final atomic parameters and equivalent isotropic thermal parameters.

Calculations were carried out on the *CDC-Cyber 175* at the University of Utrecht and on the *Univac 1110* computers at the University Computing Centre in Zagreb with the SHELX76 [19] and the X-ray system [23].

Thermogravimetric measurements were carried out on a *Cahn RG* electroanalytical balance with a heating rate of 2°/min in air. They revealed two crystalline H_2O molecules per molecule of compound; the dehydration process started at 301 °K.

Preparations. L-Prolinol was prepared according to [25]. Camphanic acid (**1**) was prepared according to [26] [27] and transformed into ethyl-ester and amide (→**5**) as already described in [11]. Hydrogenation of ethyl-ester and tosylation of primary alcohol was performed as in [10]. Zeralenone (**7**) was obtained from the fermentative plant at CRC. 14,16-Di-*O*-benzyl derivative **8** prepared according to [9], 7-*O*-acetyl derivatives **13** and **14** were obtained

Table 5. *Final Atomic Coordinates* (×10^4) *and Equivalent Isotropic Thermal Parameters* (×10^2) *for Non-H-Atoms* ($U_{eq} = \frac{1}{3}\sum_i\sum_j U_{ij} a^*_i a^*_j \vec{a}_i \vec{a}_j$)

	x	y	z	U_{eq} [Å^2]
O(21)[a]	–2263(1)	3116(4)	5101(6)	11.1(2)
O(22)[a]	–2203(2)	4960(7)	8440(10)	18.2(3)
O(1)	521(1)	9832(3)	6722(3)	6.27(6)
O(2)	–156(1)	9740(3)	5316(2)	5.55(6)
O(14)	1336(1)	8604(4)	–381(3)	8.43(8)
O(16)	1262(1)	8856(3)	5426(3)	7.50(8)
O(71)	–2157(1)	8038(3)	3891(4)	7.30(8)
O(72)	–2281(1)	10250(4)	4460(10)	18.9(3)
C(1)	314(1)	9704(3)	5398(3)	5.03(6)
C(3)	–419(1)	10015(4)	6846(4)	5.5(1)
C(4)	–922(1)	9581(4)	6484(5)	6.1(1)
C(5)	–997(1)	8007(4)	6241(5)	6.5(1)
C(6)	–1507(1)	7636(4)	5757(5)	7.1(1)
C(7)	–1645(1)	8180(4)	4087(5)	6.2(1)
C(8)	–1420(1)	7412(4)	2663(5)	6.8(1)
C(9)	–1341(1)	8292(6)	1142(5)	7.8(1)
C(10)	–983(1)	9461(5)	1349(5)	7.1(1)
C(11)	–482(1)	8981(4)	1689(5)	6.2(1)
C(12)	–131(1)	10176(4)	1915(4)	5.8(1)
C(13)	641(1)	9366(4)	893(4)	5.9(1)
C(14)	1099(1)	8855(4)	1036(5)	6.3(1)
C(15)	1297(1)	8665(4)	2566(5)	6.4(1)
C(16)	1037(1)	8996(4)	3965(4)	5.7(1)
C(31)	–378(2)	11540(4)	7318(5)	7.0(1)
C(71)	–2427(1)	9143(4)	4056(7)	9.0(2)
C(72)	–2941(1)	8837(6)	3807(9)	10.4(2)
C(121)	368(1)	9663(3)	2251(4)	5.10(6)
C(161)	562(1)	9460(3)	3839(4)	5.07(6)

[a]) H_2O molecules.

according to [6], peracetylation into **15** and **16** was performed as described in [28] and [29], respectively. Compound **17** was obtained according to [30], **18** according to [23], **19** according to [32], **22** according to [32], and **23** according to [33].

(1R,4S)-4-(Aminomethyl)-1,7,7-trimethyl-3-oxabicyclo[2.2.1]heptan-2-one (**3**). *Method A.* Camphanic amide **5** (1.97 g, 10.0 mmol) was dissolved in dry THF (20 ml) at *ca.* 40°, and $LiAlH_4$ (0.48 g, 12.5 mmol) was added portionwise over 0.5 h. Additional 10 ml of THF were added, and the mixture heated under reflux for another 0.5 h. Then, 1 ml of H_2O was added dropwise, the precipitate collected on filter and washed with THF (5 × 5 ml). The washings and filtrate were collected, evaporated, and residual oil (1.94 g) purified by chromatography on silica gel (200 g) using $CHCl_3$/MeOH 8:2. *Fractions 14–32* contained 0.14 g of unreacted **5**, *Fractions 38–48* 0.11 g of **3** (for characterization see *Method B*), and *Fractions 57-75* 0.96 of crude **6** (10 ml/fraction).

(1S,3R)-1-Hydroxy-3-(hydroxymethyl)-2,2,3-trimethylcyclopentanecarboxamide (**6**) was purified by crystallization from MeOH, m.p. 192–194°. IR: 3490, 3120 (br.), 2800–2900, 1678, 1600, 1405, 1175, 1150, 1050. ^{1}H-NMR (MeOD/CCl_4): 0.86 (*s*, 6 H); 1.00 (*s*, 3 H); 1.23–2.10 (*m*, 4 H); 2.45–2.74 (*m*, 2 H); 3.24, 3.59 (*dd*, *J* = 12, 2 H). Anal. calc. for $C_{10}H_{19}NO_3$ (201.27): C 59.68, H 9.51, N 6.72; found: C 59.95, H 9.34, N 6.72.

Method B. Soln. of the tosyl derivative **2** (677 mg, 2.0 mmol) in 30 ml of sat. NH_3/EtOH was placed in a *Parr* all-purpose bomb, under *ca.* 50 atm. NH_3 pressure, and heated at 150° for 16 h. The solvent was evaporated and crude product mixture purified by chromatography on silica gel (100 g) using $CHCl_3$/MeOH 9.5:0.5. First, 320 mg of unreacted **2**, then 128 mg (35%) of pure **3** were obtained. On crystallization from MeOH, **3** had m.p. 64–66°. IR: 3400 (br.), 2980, 2940, 2880, 1785, 1675 (br.), 1610, 1460, 1405, 1385, 1335, 1170, 1130, 1090, 1020, 915. ^{1}H-NMR ($CDCl_3$): 0.90 (*s*, 3 H); 0.91 (*s*, 3 H); 1.08 (*s*, 3 H); 1.70, 1.84 (*dd*, *J* = 8, 2 H); 1.8–1.95 (*m*, 4 H). Anal. calc. for $C_{10}H_{17}NO_2$ (183.25): C 65.55, H 9.35, N 7.65; found: C 65.38, H 9.19, N 7.85.

Diastereoselective Hydrogenation of **8**. *Method A.* Hydrogenating reagent was prepared by treatment of **3** (9.16 mg, 5.0 mmol) in 10 ml of toluene with an excess of BH_3 (10.0 mmol; prepared by the reaction of $NaBH_3$ with $BF_3 \cdot Et_2O$ complex according to [34]), initially at −60° and then at amb. temp. for 6 h. To this soln., cooled to −20° was added a soln. of ketone **8** (2.0 g, 4.0 mmol) in toluene (10 ml) with stirring, and the resulting mixture was stirred at −20° for 24 h. Consumption of **8** ($R_f \sim 0.9$) and formation of **9**/**10** ($R_f \sim 0.6$) could be followed on TLC plates *Merck RP-18 $F_{254}S$* using light petroleum/AcOEt/MeOH 8.5:1.0:0.5.

Toluene was then removed at low pressure, and the mixture was quenched by addition of 2N H_2SO_4 (60 ml). Diastereoisomeric mixture of alcohols was extracted in Et_2O (3 × 50 ml). The amine **3** was recovered by neutralization of the aq. layer. It is important to emphasize that the borane was introduced as a gas into the toluene solns.; the presence of THF or other borane-complexing ligands has deleterious effect in this reaction.

Diastereoisomeric mixture **9**/**10** thus obtained was analyzed on HPLC instrument *Perkin Elmer* serie *2/2* with *Rheodyne 7105* injector and UV/VIS *LC/55-B* detector, connected with peak area integrator *Perkin Elmer Sigma 15*, using a column *Nucleosil C_{18}* (5 m/u, 25 × 0.46 cm) and eluting system light petroleum (b.p. 60–80°) $CHCl_3$/MeOH 8.5:1.4:0.1 at the flow rate 1.6 ml/min; t_R (**9**) 8.6 min, t_R (**10**) 7.2 min. With silica gel reverse-phase plates *(Merck RP-18 $F_{254}S$)* qual. separation of **9**/**10** succeeded when the solvent mixture light petroleum/$CHCl_3$/EtOH 8.0:2.6:0.4 was used; R_f (**9**) ~ 0.65, R_f (**10**) ~ 0.70, R_f (**8**) ~ 0.9. Diastereoisomeric ratio **9**/**10** was found to be 68:32.

When the same reaction was performed at 0° and 30°, the ratio **9**/**10** dropped to 62:38, and 55:45, respectively.

Method B. In a typical procedure, keton **8** was hydrogenated with L-prolinol (**4**)·borane in THF at amb. temp. A dry 100-ml flask equipped with a side arm covered with a rubber stopper and a magnetic stirrer bar was flushed with N_2. The flask was charged with solid **4**·borane (0.70 g, 6.0 mmol). Then, dry THF (20 ml) was added to dissolve the complex and was followed by a soln. of ketone **8** (2.50 g, 5.0 mmol) in THF (30 ml) at amb. temp. over 15 min. The resulting soln. was stirred for 48 h. The workup as described in *Method A* gave a crude mixture **9**/**10** (2.16 g, 86.5%), which was analyzed by HPLC to reveal **9**/**10** (44:56).

(3S,7R)-14,16-Di-O-benzyl-3,4,5,6,7,8,9,10-octahydro-7,14,16-trihydroxy-3-methyl-1H-2-benzoxacyclotetradecin-1-one (**9**) was isolated using a prep. double column *Waters Prep-LC-System 50A* instrument prepacked with stationary phase *PRED-PAK 500-C_{18}* (5.7 × 30 cm column), and the same solvent system as used for anal. determinations. Pure sample had m.p. 114–117°, $[\alpha]_D = +52.5°$ (*c* = 1.0, MeOH). Anal. calc. for $C_{32}H_{36}O_5$ (500.64): C 76.77, H 7.25; found: C 76.49, H 7.31.

(3S,7S)-Diastereoisomer **10** had m.p. 96–98°, $[\alpha]_D = +24.7°$ (*c* = 1.0, MeOH). Anal. calc. for $C_{32}H_{36}O_5$ (500.64): C 76.77, H 7.25; found C 76.88, H 7.11.

(3S,7R)-3,4,5,6,7,8,9,10,11,12-Decahydro-5,14,16-trihydroxy-3-methyl-1H-2-benzoxacyclotetradecin-1-one (*Zeranol;* **11**). Compound **9** (650 mg, 1.3 mmol) dissolved in 15 ml of EtOH was hydrogenated in the presence of 1.2 g of *Ra*-Ni catalyst under 4-atm H_2. After 6 h, consumption of H_2 ceased, the catalyst was filtered off, filtrate evaporated to dryness, and crude **11** crystallized from i-PrOH/H_2O: It was obtained 355 mg (86%) of pure **11**, m.p. 182–183°, $[\alpha]_D = +46.3°$ (*c* = 1.0, MeOH) ([3]: m.p. 182–184°, $[\alpha]_D = +46.5°$).

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