

## CIRCULAR DICHROISM—LI<sup>1</sup>

### CIRCULAR DICHROISM OF DERIVATIVES OF HOP CONSTITUENTS CONTAINING A FIVE-MEMBERED RING

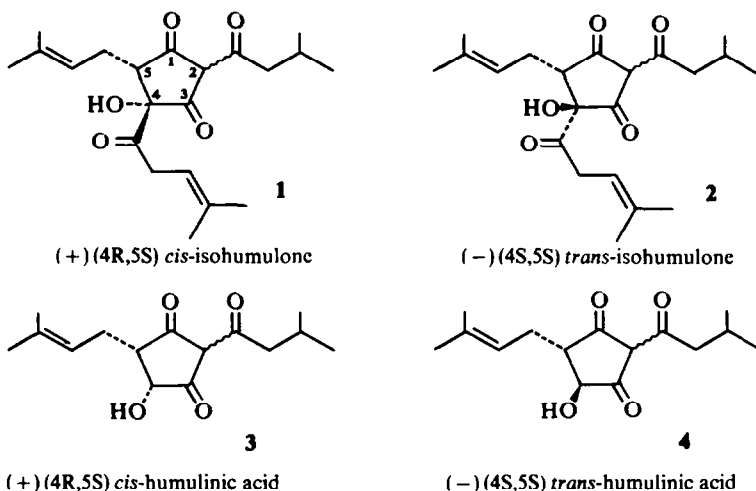
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**Abstract**—The conformation of the cyclopentenones **5** to **8** is determined from their CD-spectra. The site of enolization and the conformation of *cis*- and *trans*-isohumulone (**1** and **2**) is determined with the help of the CD-spectra, the direction of enolization for the humulinic acids **3** and **4** is tentatively determined by the same method.

THE ABSOLUTE CONFIGURATIONS of the isohumulones, essential bitter principles from beer, and the humulinic acids have recently been determined<sup>2</sup> by applying Horeau's method of partial resolution.<sup>3</sup> The *cis*-series has (4*R*,5*S*)-configuration, the *trans*-series (4*S*,5*S*)-configuration (Chart 1). In applying the notation of Cahn-Ingold-

CHART I



Prelog<sup>4</sup> the carbonyl group in the side chain at C-4 has priority over that at C-3 because the latter is almost exclusively in the enolic form as is proven by the CD spectra (see below).

Because theoretically several different enolic forms are possible, the interpretation of the CD-spectra of these compounds alone will be rather difficult. We turned,

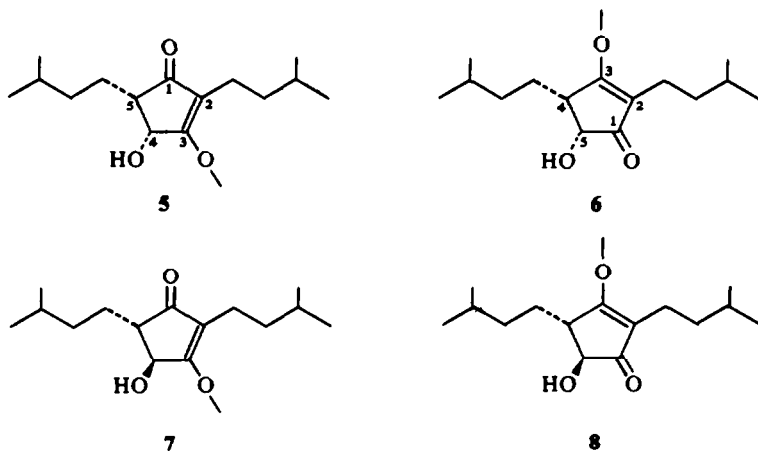
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therefore, to CD-studies of derivatives with fixed structures such as the methyl enol ethers of the dihydrodeoxo humulinic acids whose isolation was described by one of us (Chart 2).<sup>2</sup>

CHART II



The direct determination of the absolute configuration of these compounds from their CD-spectra would be possible only if their conformations could be unequivocally known. On the other hand we can determine the latter, if we base the discussion of the CD-spectra on the known absolute configuration<sup>2</sup> and apply the appropriate rules. Both the  $n \rightarrow \pi^*$ - as well as the  $\pi \rightarrow \pi^*$ -band CD has been used to correlate the sign of the Cotton effect with the chirality of cycloalkenones.<sup>5-7</sup> In general a non-coplanar transoid enone gives rise to a positive CD within the R-band if the torsion angle around the  $C(=O)-C(=C)$  bond is positive<sup>5,6</sup> whereas with the same chirality the Cotton effect is negative within the K-band.<sup>7</sup> As has been found experimentally<sup>6</sup> in case of cyclopentenones the rule for the R-band CD has to be reversed, and theoretical calculations<sup>8</sup> have supported this. It has recently been shown<sup>9</sup> that the axial hydrogens around the enone moiety seem to have a greater influence upon the sign of the K-band CD than the chirality of this system itself, therefore we confine our discussions to the more reliable R-band CD. Spectra were run in both ethanol and isooctane solution to reveal changes due to the different solvent polarity. Fig 1 shows the CD-spectra of the *cis*-derivatives, Fig 2 those of the *trans*-compounds. Their optical purities are unknown as they are derived from the natural humulinic acids which are not optically completely pure.

#### Circular dichroism of the enol ethers

The assumption that as usual the cyclopentenone ring is non-coplanar avoiding eclipsing of the substituents leads to two conformations (A and B) for each enol ether, which are shown in Fig 3 in the usual way (projection from O to C of the carbonyl group). A always leads to a positive, and B to a negative CD within the R-band.<sup>6</sup> As there are no 1:3-diaxial interactions between  $\sigma$ -bonded groups but only between a  $\sigma$ - and a  $\pi$ -bond an axial group is not *a priori* less stable than an equatorial

one, and the energy difference between the two conformers may be quite small. E.g. for  $\alpha$ -phellandrene we found an energy difference between the pseudo axial and pseudo equatorial conformer of only 0.28 kcal/mole<sup>10</sup> in favour of the latter, and at

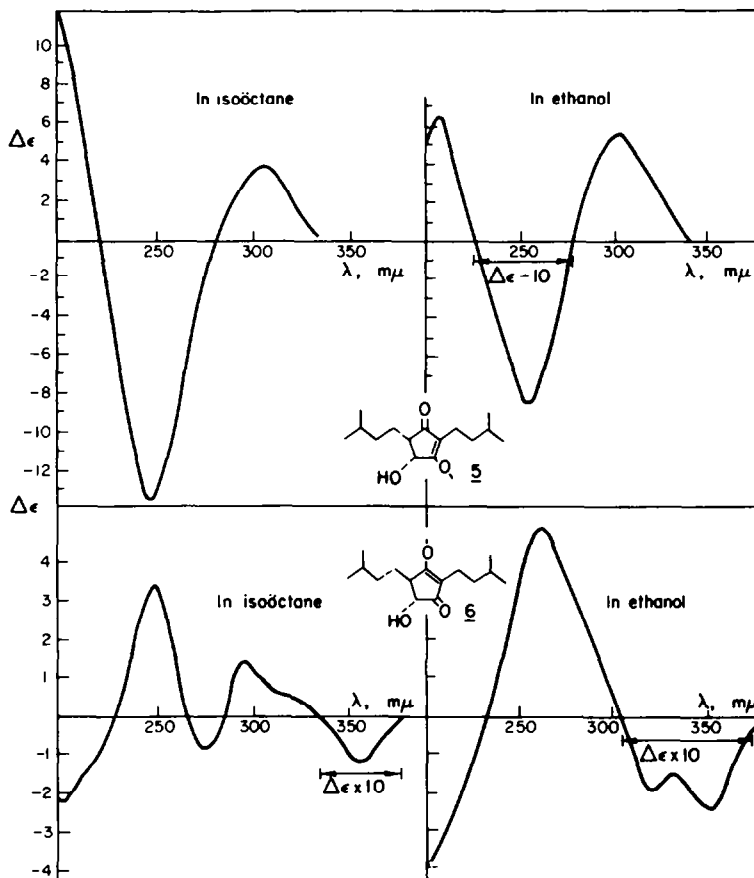


FIG 1. CD of 5 (Top) and 6 (Bottom)

room temperature the first prevails (because of a free entropy difference of 2.2 cal/degree mole). Indeed of the two *trans*-compounds (7 and 8) according to the sign of the R-band CD only 7 has both groups, (OH and isopentyl) in a quasi-diequatorial conformation at room temperature in solution, whereas 8 is present in the diaxial conformation. The difference can be explained by the fact that in 7 the small OH-group is situated next to the OMe group, whereas in 8 it is the isopentyl moiety, which obviously has less steric interaction with the MeO if in the pseudoaxial conformation. The different magnitudes of  $\Delta\epsilon$  cannot be used for correlations as both compounds may not have the same optical purity.

In the *cis*-compound, 5, showing a positive CD within the R-band conformation A

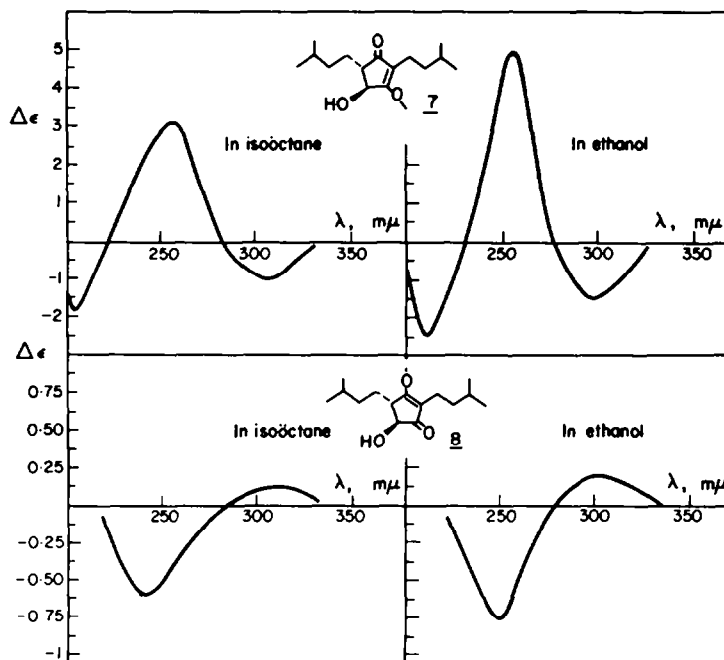


FIG 2. CD of 7 (Top) and 8 (Bottom)

with pseudoequatorial OH and pseudoaxial isopentyl must be preferred, whereas for the other *cis*-isomer **6**, in ethanol solution the situation is reversed. The substituent next to the MeO-group therefore determines the conformation, as may be expected. In isoöctane solution obviously a mixture of both conformers is present in such a ratio that both bands, the negative and the positive, are seen side by side in the spectrum. Though such "double humped" curves sometimes may be due to two series of vibronic coupling<sup>11</sup> in this case we favour the view that the CD indicates the presence of the two conformers A and B, as two CD-bands of opposite sign are also seen in the region of the K-band.

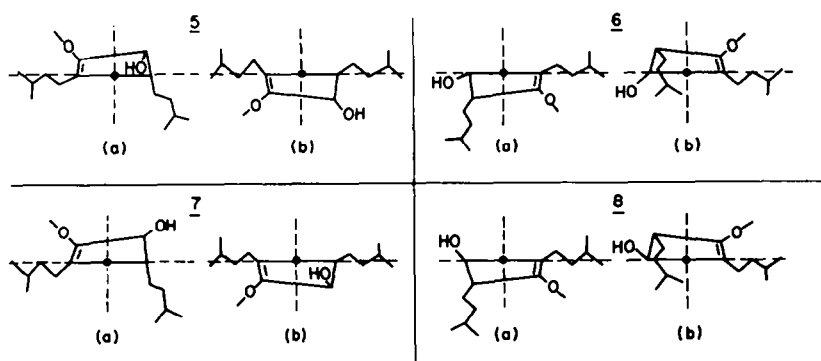


FIG 3. Octant Type Projection of 5, 6, 7, and 8

In all CD-spectra the Cotton effect within the K-band can be observed and has opposite sign to that of the R-band CD. A third CD-band opposite to that within the K-band region is found at still shorter wavelengths.

#### Circular dichroism of the free enols

Comparison of the above CD-data with those of the free enols of the ketones 1 to 4 allows the determination of the hitherto unknown site of enolization in such hop constituents. Fig 4 shows the CD of the isohumulones 1 and 2. A remarkably

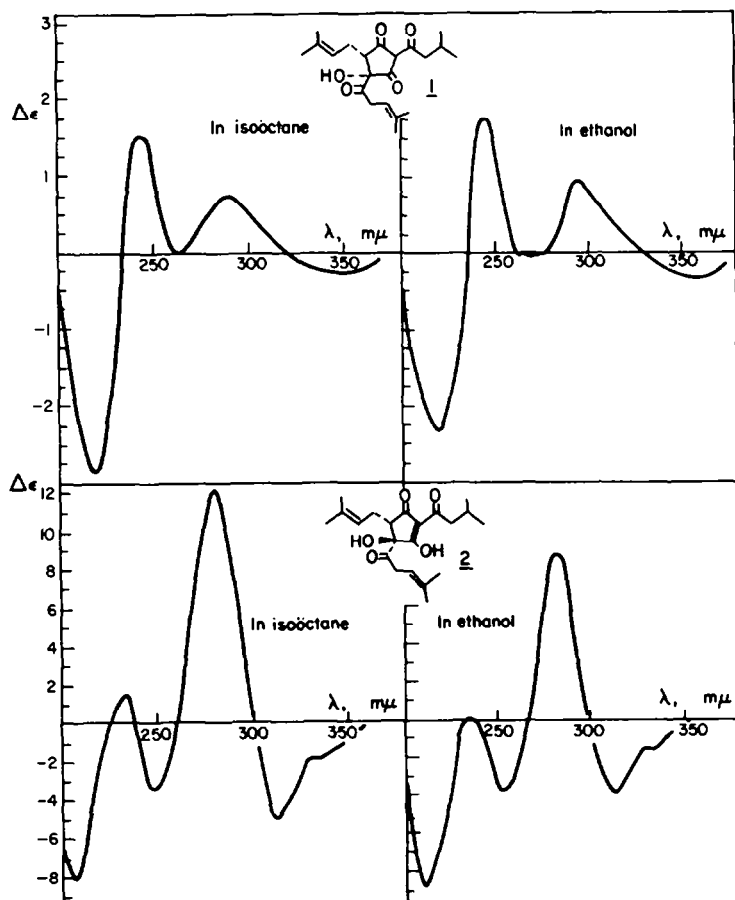
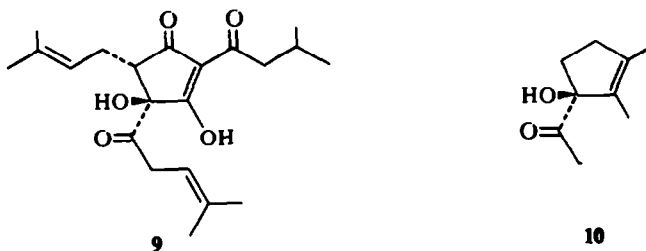


FIG 4. CD of 1 (Top) and 2 (Bottom)

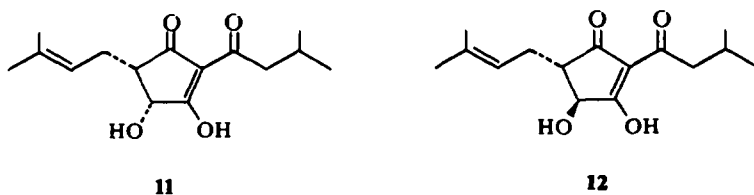
strong positive Cotton effect is observed for (4*S*,5*S*)-*trans*-isohumulone (2) at about 282 nm. This must be the R-band CD of a  $\beta,\gamma$ -unsaturated ketone in such a conformation that interaction of (localized) orbitals of the C=C- and C=O-bonds is possible.<sup>12</sup> If the cyclopentanedione moiety is enolized the saturated side chain points away from the ring and thus its carbonyl group cannot be that which gives this special interaction. This must, therefore, be the carbonyl in the 2-oxo-isohex-3-enyl

side chain and this determines the position of the double bond in the ring: carbonyl C-3 must preferably or exclusively be enolized (**9**), because it seems highly improbable that the side chain which also contains a double bond in the  $\beta,\gamma$ -position to this carbonyl is folded up only in one helical sense. Furthermore from the positive CD it is possible to deduce the conformation of this compound. The 1-oxo-iso-hex-3-enyl side chain must be positioned pseudoaxially which seems reasonable as this allows the steric interaction with the side chain at C-5 to be best avoided. The strong negative CD within the R-band of the conjugated ketone absorption is in agreement with this chirality of the ring because that C=C—C=O chromophore which is incorporated into the cyclopentenone must determine this Cotton effect and not the other one in the 1-oxo-isopentyl side chain (conjugated with the same double bond). This positive Cotton effect at 282 nm is independent proof of the earlier assignment<sup>2</sup> of the absolute configuration, as its sign is the same as in the methyl ketone derived from the aldehyde (*R*)-(+)—laurenal (**10**).<sup>13</sup>



For the *cis*-isohumulone **1** such an enhanced Cotton effect for the R-band of the  $\beta,\gamma$ -unsaturated enone chromophore should be negative because of the opposite configuration at C-4; the CD is, however, also positive in this wavelength region. If we assume the same direction of enolization within the ring then this must have the same preferred conformation for **1** and **2** as inferred from the identical negative signs of the bands at longest wavelengths. This positions the 1-oxo-iso-hex-3-enyl side chain in a pseudoequatorial conformation and indeed does not allow such a special interaction with the ring double bond to take place any more. Even if the smaller  $\Delta\epsilon$ -values would in part be due to a smaller optical purity of **1** this argumentation still remains valid.

The humulinic acids **3** and **4** are devoid of such a side chain which could give a similar effect as in **2**. Comparison of the CD-spectra (Fig 5) with those of **5** to **8** reveals, that in the region of the enone  $n \rightarrow \pi^*$ -band the CD for both the *cis*- and the *trans*-compound is similar to that of those corresponding ethers which are enolized in the same direction as the two isohumulones, **5** and **7**. We can thus tentatively assign structures **11** and **12** to the enolic forms of **3** and **4**, respectively.



These conclusions confirm the results from treatment of the dihydrodeoxo-humulinic acids with  $\text{CH}_2\text{N}_2$ , giving 85 to 90% of methyl enol ethers (5 and 7) and only 10 to 15% of the isomeric ethers (6 and 8).<sup>2</sup> However, these latter facts alone could hardly serve as unequivocal proof of the enolization situation because the

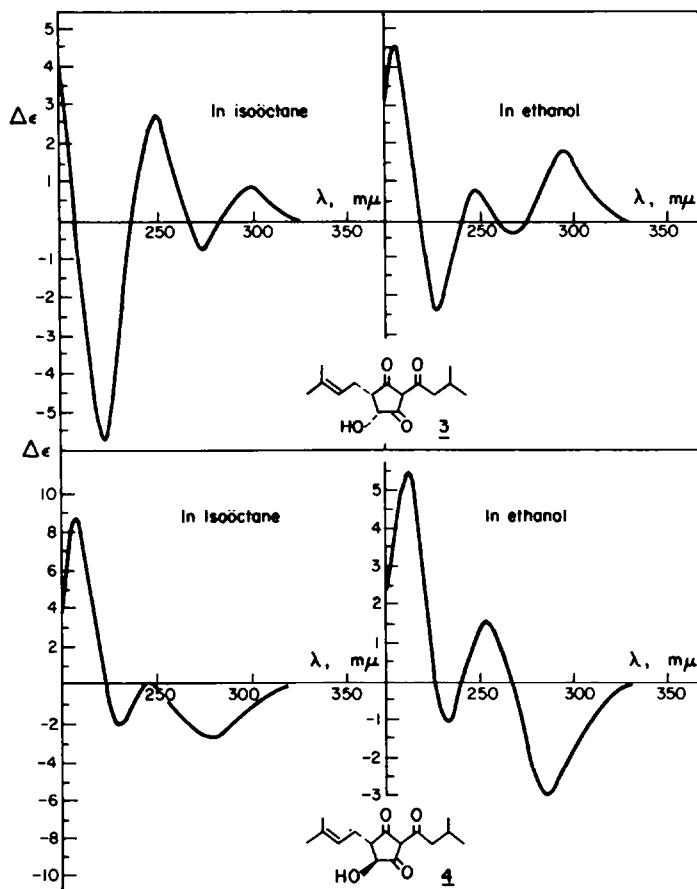


FIG 5. CD of 3 (Top) and 4 (Bottom)

carbonyl function in the C-2 side chain is lacking, and it should also be borne in mind that changes in the keto-enol equilibrium can occur on chemical reaction. The CD argument does not suffer from these disadvantages.

#### EXPERIMENTAL

All CD-spectra were recorded with a Roussel-Jouan Dichrograph model 185 in ethanol and iso-octane solution in cells of thickness between 0.01 and 10 mm at  $+20^\circ$ . The concentrations were about 1 mg/g. CD-data are given as  $\lambda(\Delta\epsilon)$  for maxima and crossover points. As optical purities are unknown, these values are minimal values.

Compound	Solvent	CD-data
1	ethanol	388 (0), 360 (-0.24), 340 (0), 294 (+1), 270 (0), 256 (0), 244 (+1.82), 234 (0), 219 (-2.30)
	iso-octane	385 (0), 355 (-0.28), 320 (0), 288 (+0.75), 244 (+1.54), 233 (0), 219 (-2.85)
2	ethanol	370 (0), 334 (-1.59), 311 (-4.02), 298 (0), 281 (+8.7), 263 (0), 253 (-3.69), 237 (0), 234 (+0.03), 231 (0), 212 (-8.84)
	iso-octane	363 (0), 333 (-1.79), 312 (-5.01), 302 (0), 281 (+12.23), 260 (0), 250 (-3.21), 238 (0), 237 (+1.84), 226 (0), 208 (-16.01)
3	ethanol	334 (0), 294 (+1.89), 275 (0), 269 (-0.25), 261 (0), 247 (+0.88), 238 (0), 228 (-2.08), 218 (0), 205 (+4.66)
	iso-octane	328 (0), 298 (+0.88), 282 (0), 273 (-0.63), 267 (0), 248 (+2.75), 232 (0), 221 (-5.70), 212 (0), 200 (+3.51)
4	ethanol	365 (0), 318 (-0.49), 286 (-3.01), 266 (0), 254 (+1.68), 240 (0), 234 (-1.05), 228 (0), 212 (+5.61)
	iso-octane	340 (0), 312 (-0.89), 280 (-2.73), 255 (0), 240 (0), 231 (-1.96), 226 (0), 209 (+8.74)
5	ethanol	335 (0), 302 (+5.92), 276 (0), 254 (-16.81), 227 (0), 208 (+6.63)
	iso-octane	342 (0), 305 (+3.63), 278 (0), 247 (-13.52), 221 (0), 202 (+10.91)
6	ethanol	395 (0), 353 (-0.24), 322 (-0.20), 307 (0), 261 (+4.89), 234 (0), 201 (-3.95)
	iso-octane	370 (0), 356 (-0.12), 344 (0), 315 (+0.60), 295 (+1.47), 286 (0), 276 (-0.77), 266 (0), 249 (+3.44), 225 (0), 201 (-2.34)
7	ethanol	335 (0), 299 (-1.50), 276 (0), 255 (+4.96), 230 (0), 211 (-2.52)
	iso-octane	340 (0), 307 (-1.02), 277 (0), 258 (+3.12), 244 (+2.25), 225 (0), 204 (-1.89)
8	ethanol	336 (0), 303 (+0.21), 288 (0), 251 (-0.75), 218 (0)
	iso-octane	343 (0), 311 (+0.12), 280 (0), 242 (-0.60), 220 (0)

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