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## ABSOLUTE CONFIGURATIONS OF QUERCUS LACTONES, (3S,4R)- AND (3S,4S)-3-METHYL-4-OCTANOLIDE, FROM OAK WOOD AND CHIROPTICAL PROPERTIES OF MONO-CYCLIC Y-LACTONES

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Absolute configurations of *Quercus* lactones were investigated by studying paramagnetic shifts of PMR spectra and the chemical correlation with 2-hydroxyhexanoic acid of known configuration. Chiroptical properties of several mono-cyclic  $\gamma$ -lactones were also studied.

Isomeric 3-methyl-4-octanolides have been identified in oak woods and aged spirits by various workers.<sup>1-4)</sup> In the previous paper,<sup>2)</sup> we tentatively named these lactones *Quercus* lactone-a and -b and assigned the *cis* form to *Quercus* lactone-a (1), the isomer eluting first in GLC on PEG 20M or UCON HB 2000, and the *trans* form to *Quercus* lactone-b (2), the second isomer from the GLC column, following the assignment of the PMR spectra of 3-methyl-4-pentanolides by Laporte *et al.*<sup>5)</sup> Kepner *et al.*<sup>3)</sup> reached the same conclusion through investigation of the PMR spectra.

Recently, Heide *et al.*<sup>6)</sup> obtained an opposing result by studying the PMR spectra of these lactones. In the PMR spectrum of 2, the C-4 proton gave a signal at  $\delta$  4.39 ppm, which had the same value as that for the C-4 proton in 4-octanolide. In the spectrum of 1, the signal of the proton was shifted to higher field,  $\delta$  3.92 ppm, because of shielding by the  $\beta$ -CH<sub>3</sub> group, *cis* positioned with respect to the proton. Therefore they concluded that 1 was of the *trans* form.

This paper concerns the reinvestigation of the structure of *Quercus* lactones,<sup>7)</sup> determination of their absolute configuration, and ORD and CD studies of some mono-cyclic γ-lactones.

The effects on the PMR spectra of *Quercus* lactones of adding paramagnetic chelates, Eu(fod)<sub>3</sub>, were studied. As shown in Fig. 1, paramagnetic shifts of two a-protons of each lactone were almost of the same value, so europium was thought to be coordinated in the lactone C-CO-O-C plane. Paramagnetic shifts of the  $\beta$ -methyl proton of 2 were greater than those of 1. Therefore, 2 can be presumed to be the



Fig. 1. Induced downfield shifts of resonances of the ring protons and  $\beta$ -methyl protons of *Quercus* lactone-a(left) and -b(right) as a function of added Eu(fod)<sub>3</sub>.

isomer the  $\beta$ -methyl proton of which adopts a quasiaxial conformation. Consequently, 2 was confirmed to be of the *cis* form as reported by Heide *et al.*<sup>6)</sup>

The absolute configuration of *Quercus* lactone-b (2) was established by the chemical correlation with 2-hydroxyhexanoic acid (8) of known configuration. Sulfenylation of the enolate of (-)-2 gave a mixture (separated by silica gel column) of (-)- trans, cis-2-methylthio-3-methyl-4-octanolide (3),  $[\alpha]_D^{15}$  -122° (c 1.01, MeOH) and (-)cis, cis-isomer (4),  $[\alpha]_D^{15}$  -29° (c 0.96, MeOH) in a 2:1 ratio. Oxidation of (-)-3 with sodium metaperiodate followed by pyrolysis at 120°C afforded (+)-5,  $[\alpha]_D^{15}$  +3.7° (c 1.10, MeOH). Compound, (+)-5, was ozonized, and the resulting ozonide was reduced by dimethyl sulfide and then hydrolyzed in water at 50°C, giving (+)-3hydroxy-2-heptanone (6),  $[\alpha]_D^{15}$  +12.5° (c 0.40, MeOH).



Reaction of L-norleucine (Z) with weakly acidic solutions of nitrous acid gave (S)-(+)-2-hydroxyhexanoic acid (B), [a]  $\frac{15}{D}$  +5.2° (c 4.61, CHCl3), which was reported by Horn *et al*.<sup>8)</sup> to have [a]  $\frac{15}{D}$  +5.6° (c 6.84, CHCl3). Methylation of (S)-(+)-B with 3 mole equivalents of methyllithium at -78°C gave (S)-(+)-B, [a]  $\frac{15}{D}$  +14.0° (c 0.40, MeOH), which showed almost the same optical rotation as the sample derived from (-)-Quercus lactone-b (2). From this interrelation, the absolute configuration of 2 was unequivocally established as (3S, 4S)-(-), since no reaction involved in the correlation affects the asymmetric center.

*Quercus* lactone-a (1) had  $[\alpha]_D^{15}$  +79° in methanol (c 1.04) and +12° in methanol containing 2% potassium hydroxide (c 0.25). From application of the Hudson lactone rule,  ${}^{9)} \triangle [\alpha]_D^{15}$  (+67°) indicated that 1 was (35,4R)-3-methyl-4-octanolide. *Quercus* lactone-b (2) had  $[\alpha]_D^{15}$  -87° in methanol (c 0.92) and -13° in methanol containing 2% potassium hydroxide (c 0.51). Therefore the configuration predicted by the rule was consistent with that established by the chemical correlation.

The UV, CD and ORD spectra of (+)-1 and (-)-2 are shown in Fig. 2 and these chiroptical data in Table 1 together with those of some mono-cyclic  $\gamma$ -lactones.<sup>10)</sup> Compound, (+)-1, showed a bisignate CD feature (at 205 nm and 227 nm) which seems to indicate conformation mobility and (-)-2 showed a positive Cotton effect (at 208 nm) in the  $n \rightarrow \pi$  \* transition region of the lactone chromophore. The sign of the Cotton effects of *Quercus* lactones in hexane was opposite to that in methanol.

Several empirical rules<sup>14-16)</sup> for lactones have been proposed, but none can consistently explain the CD spectra in the  $n \rightarrow \pi$  \* region of lactones cited in Table 1. Cervinka *et al.*<sup>17)</sup> explained the result of (S)-4-pentanolide (9) giving Cotton effects contrary to expectations based on the rules, by assuming that the  $\gamma$ -methyl group adopts the quasiaxial conformation.

On the other hand, the sign of the molecular rotations at 190 nm,  $\left[\phi\right]_{190}$ , was related to the substitution pattern

at Cy regardless of the solvent used. These relationships were closely associated with the Hudson lactone rule. The molecular rotations at 190 nm were presumed to be based upon the Cotton effects of the lactone  $\pi \rightarrow \pi^*$  transition<sup>18)</sup> in the spectral region slightly below 190 nm. The sign of the molecular rotation of Dgalacto-y-lactone (11) was contrary to expectation,



Fig. 2. UV, CD and ORD spectra of *Quercus* lactone-a (left) and -b (right) in methanol

probably because of the overlap of other transitions or the conformational change. Anyhow, in mono-cyclic γlactones which have only alkyl substituents, the sign of the molecular rotations at 190 nm is likely to indicate the substitution pattern at Cγ.

Ne	Compounds	ORD	ORD CD [φ] <sub>190</sub> Δε <sub>max</sub> λ <sub>max</sub>		UV E <sub>max</sub> λ <sub>max</sub>		<u>ΔΕ</u> Ε	Solvent
NO.		[¢] <sub>190</sub>						
	$\overline{}$	-3800	+0.40	209				Methanol
2	0 × 0 × man	-1000	+0.13	210				Hexane
	/ de la companya de l	-5300	+0.22	208	70	206	0.0032	Methanol
2	0 ~ 0 ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~	-4900	-0.08	225	445	202	0.0002	Hexane
	CH3S	-4800	-6.12	203	840	205	0.0073	Methanol
3	0 - 0	-8800	+3.09 -11.98 +6.39	250 204 250	205 1405 373	252 206 250	0.0085	Hexane
4~	CH3Sh	-13500	+5.66 -1.45	201 248	714 199	204 247	0.0079 0.0073	Methanol
<del>1</del> 0	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	-5300	-0.57	215				Methanol
ñ	но он он но	+16000	-5.48	219				Water
15	$\int$	+3800	-0.40	209				Methanol
	0== 10= 1	+1000	-0.13	210				Hexane
13	оботон	+1100	-0.07	208	եր	204	0.0016	Methanol
1~	otot	+5000	-0.12	205	84	205	0.0015	Methanol
		+3200	+0.03 +0.18	227 225	416	202	0.0004	Hexane

Table 1. Chiroptical data of some mono-cyclic γ-lactones.

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