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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 γ-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 γ-lactones were also studied.

Isomeric 3-methyl-4-octanolides have been identified in oak woods and aged spirits by various workers.1-4) In the previous paper,2) 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.* 5) Kepner *et al.* 3) reached the same conclusion through investigation of the PMR spectra.

Recently, Heide *et al.*6) 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 δ 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, δ 3.92 ppm, because of shielding by the β-CH_3 group, *cis* positioned with respect to the proton. Therefore they concluded that **1** was of the *trans* form.

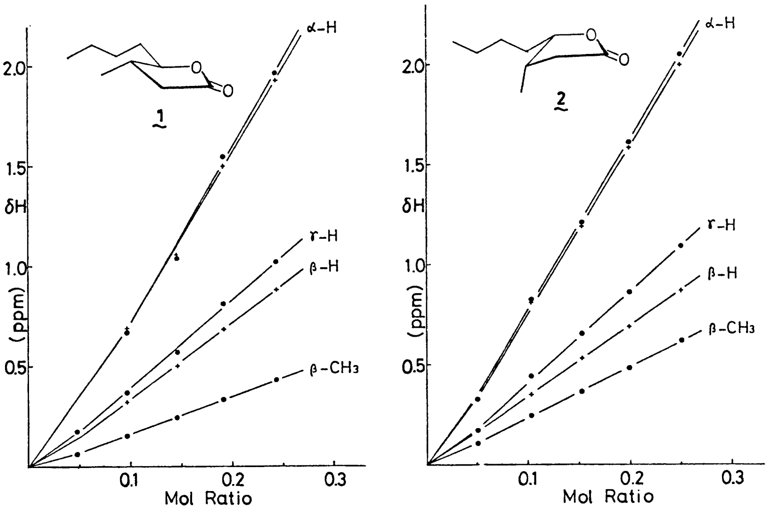
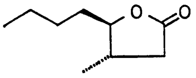


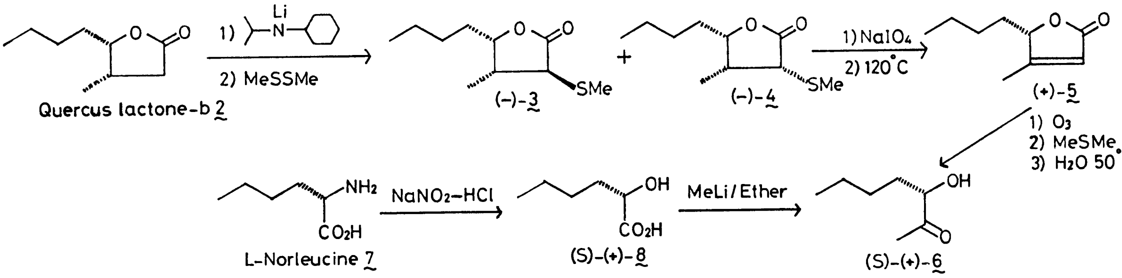
Fig. 1. Induced downfield shifts of resonances of the ring protons and β-methyl protons of *Quercus* lactone-a(left) and -b(right) as a function of added Eu$(fod)_3$.

This paper concerns the reinvestigation of the structure of *Quercus* lactones,7) 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$(fod)_3$, were studied. As shown in Fig. 1, paramagnetic shifts of two α-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 β-methyl proton of **2** were greater than those of **1**. Therefore, **2** can be presumed to be the isomer the β-methyl proton of which adopts a quasiaxial conformation. Consequently, 2 was confirmed to be of the *cis* form as reported by Heide *et al.*[6]

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), $[\alpha]^{15}_{D}$ -122° (c 1.01, MeOH) and (-)-*cis,cis*-isomer (4), $[\alpha]^{15}_{D}$ -29° (c 0.96, MeOH) in a 2 : 1 ratio. Oxidation of (-)-3 with sodium metaperiodate followed by pyrolysis at 120°C afforded (+)-5, $[\alpha]^{15}_{D}$ +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 (+)-3-hydroxy-2-heptanone (6), $[\alpha]^{15}_{D}$ +12.5° (c 0.40, MeOH).


Quercus lactone-a 1



Reaction of L-norleucine (7) with weakly acidic solutions of nitrous acid gave (S)-(+)-2-hydroxyhexanoic acid (8), $[\alpha]^{15}_{D}$ +5.2° (c 4.61, $CHCl_3$), which was reported by Horn *et al.*[8] to have $[\alpha]^{15}_{D}$ +5.6° (c 6.84, $CHCl_3$). Methylation of (S)-(+)-8 with 3 mole equivalents of methyllithium at -78°C gave (S)-(+)-6, $[\alpha]^{15}_{D}$ +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 $[\alpha]^{15}_{D}$ +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] $\Delta[\alpha]^{15}_{D}$ (+67°) indicated that 1 was (3S,4R)-3-methyl-4-octanolide. *Quercus* lactone-b (2) had $[\alpha]^{15}_{D}$ -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 γ-lactones.[10] 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[14-16] 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.*[17] explained the result of (S)-4-pentanolide (9) giving Cotton effects contrary to expectations based on the rules, by assuming that the γ-methyl group adopts the quasiaxial conformation.

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

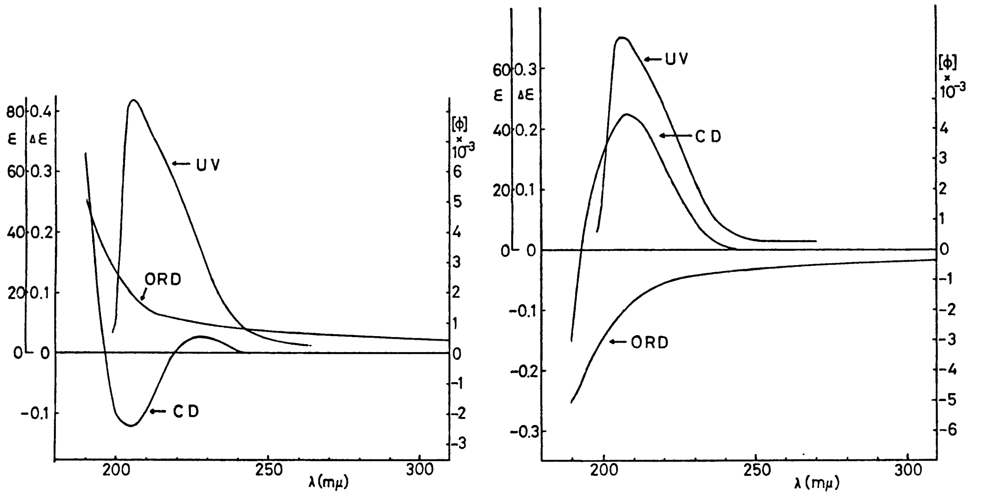
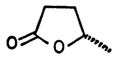
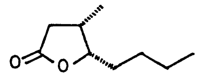
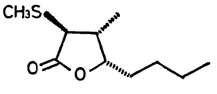
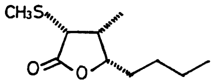
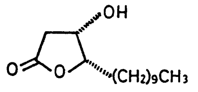
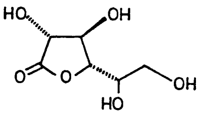
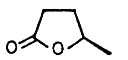
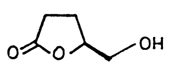
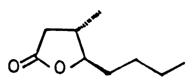


Fig. 2. UV, CD and ORD spectra of *Quercus* lactone-a (left) and -b (right) in methanol

at Cγ 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 π→ π* transition[18] in the spectral region slightly below 190 nm. The sign of the molecular rotation of D-galacto-γ-lactone (11) was contrary to expectation, probably because of the overlap of other transitions or the conformational change. Anyhow, in mono-cyclic γ-lactones which have only alkyl substituents, the sign of the molecular rotations at 190 nm is likely to indicate the substitution pattern at Cγ.

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

No.	Compounds	ORD	CD		UV		$\left\|\frac{\Delta\varepsilon}{\varepsilon}\right\|$	Solvent
		$[\phi]_{190}$	$\Delta\varepsilon_{max}$	λ_{max}	ε_{max}	λ_{max}		
9		-3800	+0.40	209				Methanol
		-1000	+0.13	210				Hexane
2		-5300	+0.22	208	70	206	0.0032	Methanol
		-4900	-0.08	225	445	202	0.0002	Hexane
3		-4800	-6.12	203	840	205	0.0073	Methanol
			+3.09	250	285	252	0.0108	
		-8800	-11.98	204	1405	206	0.0085	Hexane
			+6.39	250	373	250	0.0171	
4		-13500	+5.66	201	714	204	0.0079	Methanol
			-1.45	248	199	247	0.0073	
10		-5300	-0.57	215				Methanol
11		+16000	-5.48	219				Water
12		+3800	-0.40	209				Methanol
		+1000	-0.13	210				Hexane
13		+1100	-0.07	208	44	204	0.0016	Methanol
1		+5000	-0.12	205	84	205	0.0015	Methanol
			+0.03	227				
		+3200	+0.18	225	416	202	0.0004	Hexane

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