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TWO NEW KHELLACTONE ESTERS FROM *PEUCEDANUM JAPONICUM* THUNB.

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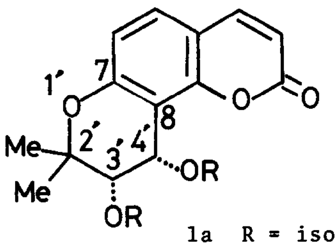
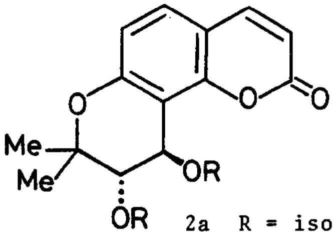
During the investigation of the chemical constituents of *Peucedanum japonicum* Thunb. (Umbelliferae), a chinese herbs used in Taiwan, two new khellactone esters have been isolated from the n-hexane extract. We wish to report the full structure and the conformational study of these compounds.

Silica gel chromatography of the n-hexane extract of whole herbs have afforded two crystalline compounds 1a; $C_{24}H_{30}O_7$, m.p. 88-89°, $[\alpha]_D$ -38.8°(c 0.1, $CHCl_3$), and 1d; $C_{24}H_{26}O_7$, m.p. 112-113°, $[\alpha]_D$ -47.7°(c 0.1, $CHCl_3$). The typical uv absorption of 1a [λ_{max}^{EtOH} 246(logε 3.59),256(3.54), 300sh(3.94) and 324(4.10) nm] showed the presence of 7-oxycoumarin moiety.[1] The ir and nmr spectra of 1a[ν_{max}^{KBr} 1760-1738, 1630, 1610, 1573 and 1488 cm^{-1}, $\delta_{ppm}^{CDCl_3}$ 0.98(12H,d,J=7.0 Hz) , 1.43, 1.46 (each 3H,s,geminal dimethyls at C-2'), 2.19(6H,br.s), 5.34, 6.55(each 1H,d,J=5.0 Hz,AB-type) 6.80, 7.37(each 1H,d,J=8.5 Hz,AB-type), 6.24 and 7.60(each 1H,d, J=9.5 Hz,AB-type)] suggested that the compound 1a was a khellactone ester.[2] Hydrolysis of 1a with 5 % aqueous sodium hydroxide afforded isovaleric acid and two isomeric diols 1b; $C_{14}H_{14}O_5$, m.p. 172-173°, $[\alpha]_D$ -83.3°, $\nu_{max}^{CHCl_3}$ 3600, 3480 and 1720 cm^{-1}, $\delta_{ppm}^{CDCl_3}$ 1.43, 1.46(each 3H,s), 3.87 and 5.24(each 1H,d,J=5.0 Hz) and 2b; $C_{14}H_{14}O_5$, m.p. 185-186°, $[\alpha]_D$ +19.2°, $\nu_{max}^{CHCl_3}$ 3600, 3430 and 1720 cm^{-1}, $\delta_{ppm}^{CDCl_3}$ 1.33, 1.55(each 3H,s), 3.87 and 5.02(each 1H,d,J=6.8 Hz). These physical properties of the isomeric diols 1b and 2b coincided with those of the previously known (+)-cis-khellactone 3a; m.p. 174-175°, $[\alpha]_D$ +80.9°, and (-)-trans-khellactone 4a; m.p. 185-186°, $[\alpha]_D$ -18.0°, except for the signs of their optical rotations,[2] respectively. Formation of a mixture of the diols was known to be a consequence of the epimerization at the benzylic 4'-position during the alkaline hydrolysis of the natural khellactone esters.[2,3] Thus the epimeric diols 1b and 2b were shown to be (-)-cis-khellactone and (+)-trans-khellactone, respectively, which were the antipodal khellactones initially encountered in natural source. Therefore the compound 1a was ascribable to a diester of isovaleric acid and one of these khellactones. Assignment of the cis configuration to the native ester 1a was confirmed by acylating both khellactones with isovaleryl chloride. Reaction of (-)-cis-khellactone 1b with isovaleryl chloride in pyridine afforded cis-diisovalerylkhellactone 1a whose physical properties were identical with those of the natural product in every respect, on the other hand the similar reaction of (+)-trans-khellactone 2b afforded trans-diisovalerylkhellactone 2a; $[\alpha]_D$ +5.8°, $\delta_{ppm}^{CDCl_3}$ 1.37, 1.45(each 3H,s), 5.30 and 6.21(each 1H,d,J=4.0 Hz) which was different from the natural ester. Thus the structure of the compound 1a was established as cis-diisovalerylkhellactone.



1a R = isovaleryl
1b R = H
1c R = p-chlorobenzoyl
1d R = senecioyl



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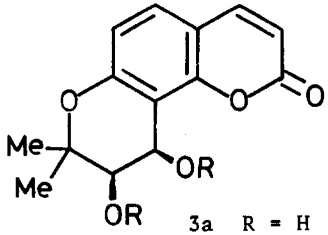
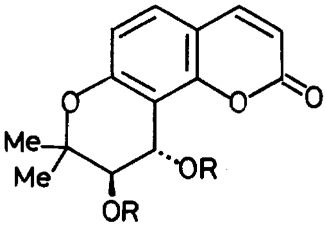
2c R = p-chlorobenzoyl



3a R = H
3b R = senecioyl



4a R = H

With respect to the absolute configuration of khellactones, Lemmich et al.[4] clarified that (+)-cis-khellactone 3a had 3'(R) and 4'(R) on the basis of the chemical conversion of the khellactone and its derivatives into dihydrolomatin, whose absolute configuration 3'(R) had been established.[5] Thus the absolute configuration of (-)-cis-khellactone 1b, an antipode of (+)-cis-khellactone 3a, was deduced to 3'(S), 4'(S) and therefore the full structure of the native diester was shown to be 3'(S),4'(S)-diisovalerylkhellactone as represented as 1a.

The second compound 1d showed similar spectra to those of 1a; λ_{max}^{EtOH} 245(3.95), 256(3.78), 298sh(3.98) and 324(4.17)nm, $\delta_{ppm}^{CDCl_3}$ 1.43, 1.46(each 3H,s), 1.89(6H,s),2.17 (6H,br.s), 5.65(2H,br.s), 5.36 and 6.63(each 1H,d,J=5.0 Hz). Alkaline hydrolysis of 1d gave also (-)-cis-khellactone 1b and (+)-trans-khellactone 2b, in addition to senecioic acid as only separable acidic compound. Thus the structure of 1d was represented as 3'(S),4'(S)-disenecioylkhellactone, which was an antipode of (+)-cis-disenecioylkhellactone 3b, isolated from *Seseli libanotis* (L.) Koch.[6]

Lemmich et al.[6] described half chair or distorted half chair conformations for the khellactone derivatives on the basis of nmr study. Now we proposed the conformation of 1a, 1c and 1d as shown in (I) by an application of the dibenzoate chirality rule[7,8] and nmr analysis. The cd spectrum of cis-di-p-chlorobenzoylkhellactone 1c; [λ_{max}^{EtOH} 241(4.46),285sh (3.81), 298sh(3.89) and 324 (4.04)nm , $[\alpha]_D$ -114.3°, $\delta_{ppm}^{CDCl_3}$ 1.51, 1.61(each 3H,s), 5.66, 6.93(each 1H,d,J=5.0 Hz), 7.34 and 7.84(each 4H,d,J=9.0 Hz)], which was synthesized by the acylation of 1b with p-chlorobenzoyl chloride, showed a positive Cotton effect at 250 nm ($\Delta\varepsilon$ +59.2)* as shown in Figure 1. It indicates that the vicinal p-chlorobenzoyloxy groups at C-3' and C-4' in 1c have a positive chirality. Two possible conformations (I) and (II) are available for cis-khellactone derivatives 1; the aromatic carbons(7- and 8-position) and two adjacent atoms (O-1' and C-4') are in plane, whereas the atoms on the other side (C-2' and C-3') are staggered. In the case of (I), the carbon atom at C-3' situates above the plane, so that the substituents at 3' and 4' have a positive chirality, while in (II) which have the negative chirality, the carbon atom at C-3' comes to below the plane. The obser-

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* The transition at 324 nm due to coumarin chromophor was not affected by the dipole-dipole coupling with the benzoate groups because the band is located far from the benzoate transition.

vation of cd measurement indicated clearly that the conformation (Ic) was preferred for the dibenzoate 1c, and the possibility of the conformational equilibrium between the two conformations reported by Lemmich et al.[6] was excluded. Thus the conformational structures for 1a and 1d are similarly represented as (Ia) and (Id), respectively, since the value of the vicinal coupling constant (3' and 4'-H, J=5.0 Hz) in these compounds are same as that of 1c, indicating these compounds in similar conformation. On the other hand, trans-di-p-chlorobenzoylkhellactone 2c [λ_{max}^{EtOH} 245(4.49), 285sh(3.81), 298sh(3.89), and 324(4.04) nm, $[\alpha]_D$ -204.6°, $\delta_{ppm}^{CDCl_3}$ 1.50, 1.60 (each 3H,s), 5.63, 6.58 (each 1H,d,J=3.7 Hz), 7.34 and 7.93 (each 4H,d,J=9.0 Hz)] showed a negative Cotton effect at 249 nm ($\Delta\varepsilon$ -56.5) in cd spectrum (Figure 1), which indicated the vicinal acyl groups adopted a negative chirality.

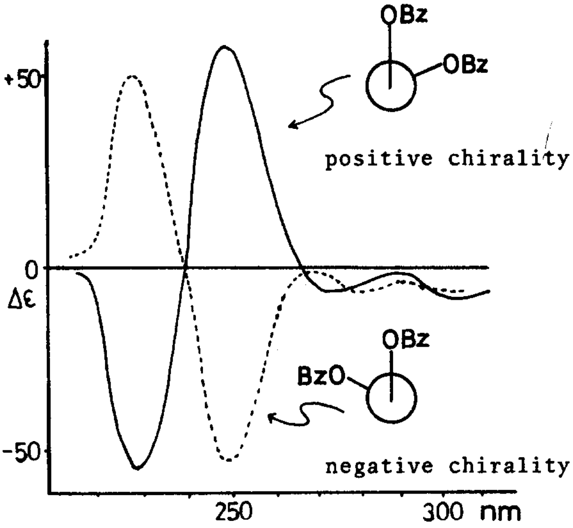
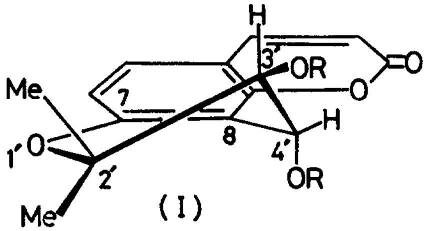


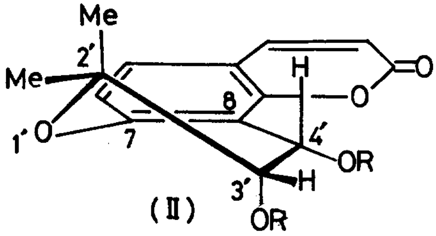
Figure 1 The cd spectra of 1c and 2c

The solid line; 1c

The broken line; 2c



(I)



(II)

a; R = isovaleryl

c; R = p-chlorobenzoyl

d; R = senecioyl

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