Communications to the Editor

Chem. Pharm. Bull.
33(5)2179—2182(1985)

THE ABSOLUTE CONFIGURATION OF CURDIONE AND THE STEREOSTRUCTURE OF CURCUMALACTONE FROM *CURCUMA WENYUJIN*

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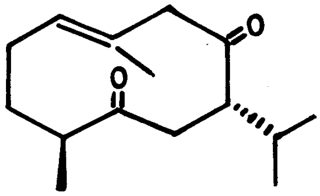
The absolute configuration of curdione isolated from *Curcuma wenyujin* was determined as **1** on the basis of its CD spectra and the X-ray diffraction of the *p*-bromobenzoate of 8αH-dihydrocurdione (2a). The absolute stereostructure of a new spirocyclopentanolide, curcumalactone occuring in the titled plant, was deduced as **3** based on its direct X-ray analysis and the biomimetic transformation of **1** to **3**.

KEYWORDS——curdione; germacranoid; curcumalactone; spirocyclopentanolide; *Curcuma wenyujin*; Zingiberaceae; absolute structure; CD; X-ray diffraction; ^{1}H-NMR (400 MHz)

In our preceding paper,2) the absolute stereostructure of curdione (1), isolated from *Curcuma wenyujin* has recently been deduced on the basis of its direct correlation with curcumol, whose complete structure had been determined.3) This communication describes the determination of the absolute configuration of **1** on the basis of CD spectral measurements and X-ray diffraction of the *p*-bromobenzoate (2b) of 8αH-dihydrocurdione (2a). Also, the absolute stereostructure of a novel sesquiterpenolide, referred to curcumalactone (3), which was isolated from the essential oil of the title plant, is also elucidated based on its direct X-ray analysis and the biomimetic conversion of **1** into **3**.

Concerning the absolute configuration of **1**, the circular dichroism (CD) spectra in methanol, cyclohexane and dioxane showed a strong positive Cotton effect at 312 nm ($[\theta]$ +75.259; MeOH). Since this must be attributed to the β, γ-unsaturated ketone moiety in **1**, the absolute structure should be represented as **1** rather than its mirror image, when an extended octant rule is applied.4)

In order to confirm unambiguously the absolute configuration of **1**, 8αH-dihydrocurdione (2a) was prepared, and its *p*-bromobenzoate (2b) was subject to the X-ray diffraction study mentioned below. Stereoselective reduction ($LiAlH_4$/ether, r.t. 10 min.) of **1** afforded ketol (2a).5) $C_{15}H_{26}O_2$; mp 163-164°C; $[\alpha]_D^{24}$ +3.07°(c, 3.58; $CHCl_3$); IR $\tilde{\nu}_{max}^{KBr}$ cm^{-1}: 3474 (OH), 1698 (C=O); EI-MS m/z 238 (M^+); CI-MS m/z 239 (MH^+); high resolution (HR) MS m/z 238.1932 (Theor. 238.1932), ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 0.76, 0.96 (3H x 2, each d, J = 6.8, 12, 13-H), 0.85 (3H, d, J = 7.1, 14-H), 1.76 (3H, s, 15-H), 3.67 (1H, m, 8-H), 4.94 (1H, d, J = 8.3, 1-H). The



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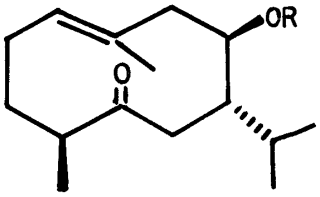
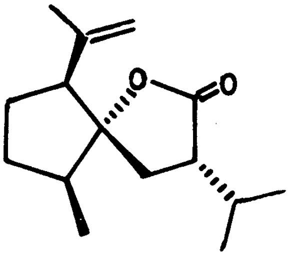


2a (R=H)
2b (R=COC$_6$H$_4$Br)



3

p-bromobenzoate (2b) of 2a was prepared by *p*-BrC$_6$H$_4$COCl/CH$_2$Cl$_2$ using 4-dimethylaminopyridine at room temperature. C$_{22}$H$_{29}$O$_3$Br; mp 132-134°C; $[\alpha]_D^{24}$ -23.52°(c, 0.765; CHCl$_3$); IR ν_{max}^{KBr} cm^{-1}: 1720 (benzoate C=O), 1595 (arom.); ^{1}H-NMR (CDCl$_3$, 200 MHz) δ: 0.67, 0.86, 1.01 (3H x 3, each d, J = 7.0, 12, 13, 14-CH$_3$), 1.86 (3H, s, 14-H), 5.04 (1H, d, J = 10, 1-H), 6.21 (1H, d,d,d, J = 10, J = 10, J = 4, 8-H), 7.66 & 7.97 (2H x 2, each d, J = 8, arom-H). The crystal data are as follows: C$_{22}$H$_{29}$O$_3$Br, MW 421.4, monoclinic, space group P2$_1$, lattice constant a = 15.394(8), b = 5.451(3), c = 14.225(8) Å, β = 115.61(6)°, U = 1076 Å^3, Z = 2, D$_{calc}$ = 1.300 gcm^{-3}. A fine crystal of approximate dimensions 0.03 x 0.01 x 0.5 mm was chosen for the X-ray study. Of the total of 2343 reflections observed within the 2θ range of 6° through 70°, 1620 reflections were crystallographically independent and 519 were Friedel reflections. The remaining 204 were equivalent reflections which agreed with the original ones with an approximate R' value$^{6)}$ of 0.03. The R' value$^{6)}$ for Fiedel reflections was 0.055. The structure was determined by the heavy atom method and refined by the block-diagonal matrix least-squares method to an R value of 0.06. All the hydrogen atoms were included with isotropic temperature factors. The absolute configuration was determined by the anomalous dispersion method allowing for the dispersion terms of Br, O and C atoms for CuK$_\alpha$ radiation. Of the total of 135 Friedel pairs, for which the value $||F_o(hkl)|-|F_o(h\bar{k}l)||$ was estimated to be greater than 2δ(F$_o$), 120 pairs showed the same configuration as given in Fig. 1. The final refinement in which the dispersion corrections were adequately made, gave the R value of 0.053.$^{7)}$ Hence the absolute structure of 2b was deduced as depicted in Fig. 1. The absolute configuration of 1 thus determined definitely is in agreement with that deduced from the CD analysis of 1 mentioned above.

Furthermore, a novel spirocyclopentanolide, curcumalactone (3) was found in

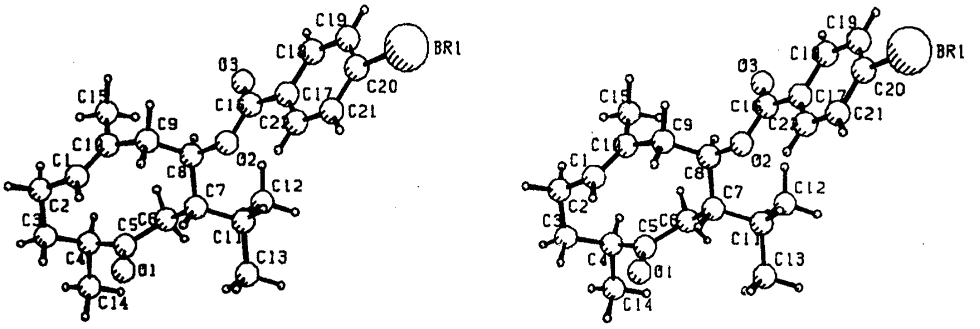
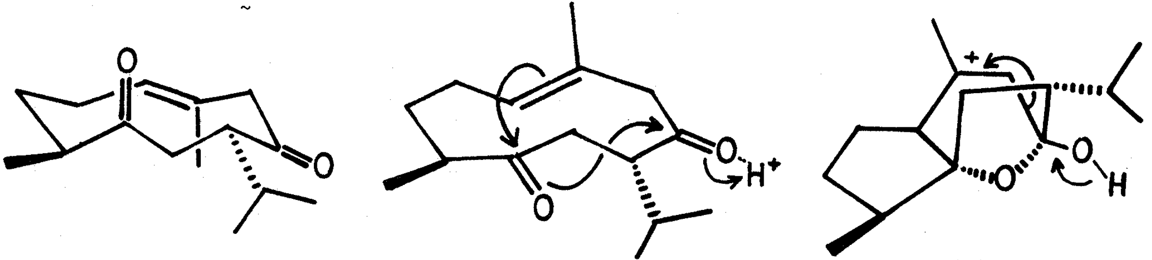


Fig. 1. Stereoview of *p*-Bromobenzoate (2b) of 8αH-Dihydrocurdione (2a)

the essential oil of the title plant.[8] It is of special value to note that 3 was stereoselectively and exclusively transformed from 1 in chloroform solution at room temperature, especially in the presence of a catalytic amount of hydrochloric acid.[9,10] $C_{15}H_{24}O_2$; mp 34-36°C; $[\alpha]_D^{24}$ -11.07°(c, 3.43; $CHCl_3$); IR ν_{max}^{KBr} cm^{-1}: 3085, 1648 ($C=CH_2$), 1773 (lactone); EI-MS m/z 236 (M^+); CI-MS m/z 237 (MH^+); HR-MS m/z 236.1791 (Theor. 236.1770); ^1H-NMR ($CDCl_3$, 400 MHz) δ: 0.90, 0.94, 0.98 (3H x 3, each d, J = 6.8, 12, 13, 14-H), 1.19 (1H, m, 3-H), 1.75 (2H, m, 2-H), 1.80 (3H, s, 15-H), 1.81, 1.84 (2H, m, 6-H), 1.93 (1H, m, 3-H), 2.18 (1H, m, 11-H), 2.42 (1H, m, 4-H), 2.57 (1H, d,d,d, J = 4.88, J = 10.25, J = 10.25, 7-H), 2.75 (1H, d, d, J = 8.8, J = 11.5, 1-H), 4.91 (1H, s, 9a-H), 4.99 (1H, t, J = 1.5, 9b-H). The structure was determined by direct X-ray analysis of 3. The crystal data are as follows: $C_{15}H_{24}O_2$, MW = 236.4, orthorhombic, space group $P2_12_12_1$, lattice constant a = 13.357(9), b = 17.272(9), c = 6.341(4) Å, U = 1463 $Å^3$, Z = 4, D_{calc} = 1.073 gcm^{-3}. A small needle crystal was selected for diffraction study. Of the total of 1490 reflections within 2θ range of 6° through 130°, 1014 were above the 2σ (I) level and were used for the structure determination. The crystal structure was solved by the direct method and refined by the method of blockdiagonal least-squares. Seventeen heavier atoms and all of the 24 hydrogen atoms were located and their parameters were refined to an R value of 0.072.[7] Fig. 2 shows the molecular structure of 3.



(A) (B) (C)

Chart 1. A Possible Biogenetic Pathway of Curcumalactone (3) from Curdione (1)

From the viewpoint of the elucidation of the absolute strucutre of 1 and the relative stereochemistry of 3, the facile conversion of 1 into 3 seems to involve the following steric course as shown in Chart 1. First, the alternative conformation of 1 (B)(C(5)=O/C(10)-CH_3: anti) as a possible intermediate would be formed by spontaneous inversions of C(4)-C(5)-C(6) and C(2)-C(1)-C(10) segments in the original stable conformation of 1 (A)(C(5)=O/C(10)-CH_3: anti).[2] The second possible cationic intermediate (C), being derived concomitantly, by the similar regio- and stereospecific concerted manner as in the formation of curcumol,[3] should create the target spiro-lactone (3) via a specifically stereoselective course induced by deprotonation and subsequent C(8)-C(9)-bond cleavage in a hypothetical biogenetic pathway.

Consequently, the stereospecific transformation of 3 from 1 under a very mild biomimetic condition and the co-existence of both 1 and 3 in the essential oil indicate that the absolute stereostructure of 3 may be designated as above rather than its mirror image. Thus, the complete stereostructures of curdione (1) and its possible biogenetic congeners, i.e. curcumalactone (3) and curcumol,[3] have been established. From the comprehensive point of view of our extensive studies[2, 3] including this paper, the absolute stereostructures of dehydrocurdione,[12a] one

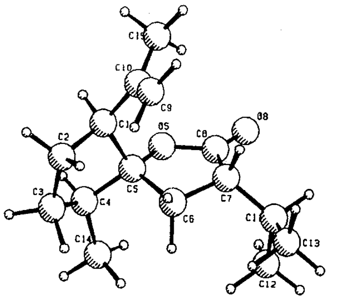


Fig. 2. Perspective View of Cucumalactone (3)

of dehydrospirolactones,[10] isocurcumenol[12b] and curcumenol[12c] (which are closely related to the respective 7α-isopropyl analogues, that is, curdione (1),[2,3] curcumalactone (3), curcumol,[2] and $\Delta^{10(15)}$-curcumol[2]) can automatically be defined regardless of a lost chiral centre at C(7).

A further study for the conclusive proof of the absolute configuration of **3**, which is estimated as above, is now in progress.

ACKNOWLEDGEMENTS One of the authors (S.I.) acknowledges a research grant from the Miyata Academic Prize partly used for this work. The authors are gratefull to Dr. Akita of The Physical and Chemical Institute and Dr. R. Moroi of Daiichi Co., Ltd for NMR spectral measurements. Thanks are also due to Mr. H. Yamanaka and Miss S. Takei of the Joint Laboratory, School of Medicine, Keio University, for MS and IR spectral measurements.

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5) Sodium borohydride reduction of 1 gave an oily ketol[†] ($[\alpha]_D^{24}$ +74.5° (c, 1.8; $CHCl_3$). This may be assigned to 8βH-epimer of 2a in the light of the present study. [†]Hikino, Y. Sakurai, H. Takahashi and T. Takemoto, Chem. Pharm. Bull., 15, 1390 (1960).
6) $R' = \Sigma||FO1|-|FO2|| / \Sigma|FO1|$.
7) The final atom parameters will be included in the Cambridge Crystallographic Data file and the list of structure factors may be obtained upon request from one of the authors (Y.I.).
8) Repeated silicagel chromatography of the essential oil (500 mg) using pentane/ether (100:1) as an eluent provided 2 mg of 3 (80 % purity), whose GC/MS fragmentation pattern was comletely identical with that of an authentic sample of 3 derived from 1 as described in the text.
9) A cyclohexanolide with the identical composition, whose structure does not obey the conventional isoprene rule, was obtained on treatment of 1 with sulfuric acid according to unpublished data by X-U. Wu, J-H. Xie and Y-T. Guo [private communication from one of the authors (Y-T Guo)].
10) Two isomers of 7(11)-dehydrospirolactone were isolated from the dried rhizomes of C. zedoariae, and also obtained by acid catalyzed cyclization of 1 [Y. Shiobara, T. Iwata, H. Yasuda, Y. Asakawa, M. Kodama and T. Takemoto, 28th annual meeting of Perfume, Essential Oil and Terpene, Kanazawa, Oct. 13-15, Abstract papers, p. 271 (1984)]. The stereochemistry of one of the isomers proposed by these authors coincides with 3 with respect to each configuration at C(1)(αH), C(4)(αH) and C(5)(αO) regardless of the chirality at C(7)(αH). Accordingly, another 7(11)-dehydroisomer should be assigned to 1βH-epimer as they stated.
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(Received March 30, 1985)