Curcumol and Its One-Step Formation from Curdione

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The absolute stereochemistry of curcumol (**1**) is confirmed on the basis of the spectroscopic data. The existence of two conformations in curdione (**4**) is revealed by nOe experiments at ambient temperature. One-step conversion of **4** into **1** stereospecifically proceeds *via* the ene-reaction without epimerization at any asymmetric center in **4**.

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An antitumor sesquiterpene was isolated from *Curcuma aromatica* Salisb. by us (Chinese group) [1] and identified to be curcumol (**1**) isolated from *C. zedoaria* Roscoe (*Zingiberaceae*) by Hikino *et al.* [2] by comparison of the physicochemical properties. The latter group decided the gross structure of **1** to be formula **1a** on the basis of the chemical reactions and the spectroscopic data [2]. Recently, Inayama *et al.* [3] determined the absolute stereochemistry of **1** to be formula **1b** by X-ray analysis. This paper is concerned with an approach to **1b** by means of spectroscopy (^{1}H, ^{13}C nmr and cd) and also its one-step formation from sesquiterpene curdione (**4**) (*vide infra*) isolated from *Curcuma* sp.

Absolute Stereochemistry of Curcumol (1).

The complete, unambiguous assignments of protons and carbons in **1** were smoothly made without any comment by ^{1}H-^{1}H and ^{1}H-^{13}C COSY techniques in the nmr spectrum (Table I). These data were in accord with **1a**. The relative stereochemistry of **1** was confirmed by nOe experiments (Table II). Irradiation of 4-H and 6α-H showed nOe's on 1-H, suggesting that 1-H, 4-H and the 5-6 bond are *cis* with respect to A ring, and the A/B ring juncture is *cis*. If it is assumed that B ring adopts a chair conformation (not unreasonable), an ethylene bridge between the 5- and 8-positions led to that the 5-6 and 7-8 bonds bear "1,3-diaxial" relationship, and 1-H is oriented equatorial with respect to B ring. NOe's were also observed among 1-H, 9α-H, 12-H$_3$ (Me), and 13-H$_3$ (Me), suggesting the 7-isopropyl group to be oriented *endo*(α). This situation can be seen in a Dreiding model **1c**. At this stage, the relative stereochemistry of **1** was made clear.

The ketone **2** obtained by ozonolysis of **1** showed a negative Cotton effect, $[\theta]^{20}_{292}$ −1430 (dioxane), in the cd spectrum. Thus, the absolute stereochemistry of **1** should be represented to be **1b** (1*S*,4*S*,5*S*,7*S*,8*R*) by application of the octant rule to **2** [4]. It is worth noting that the cd spectrum of **1** exhibited a positive Cotton effect, $[\theta]^{25}_{202}$ +19100 (methanol), which is explained by the left-hand rule of olefin according to Scott *et al.* [5] (Figure 1).

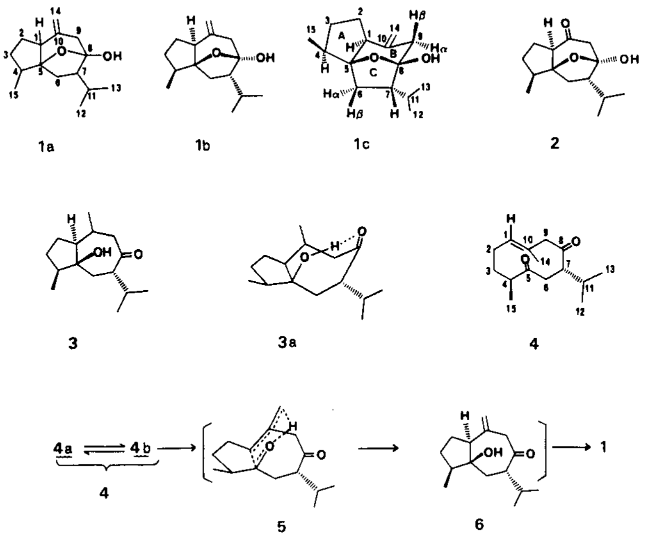


Chart 1

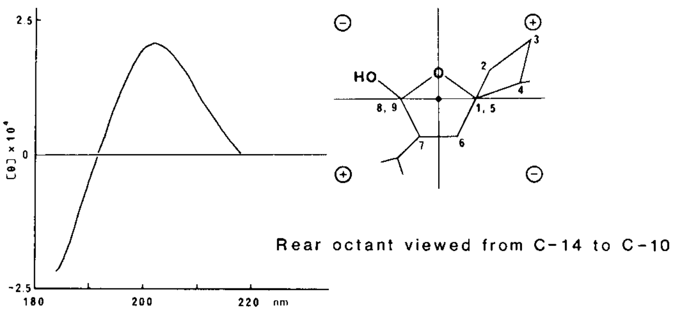
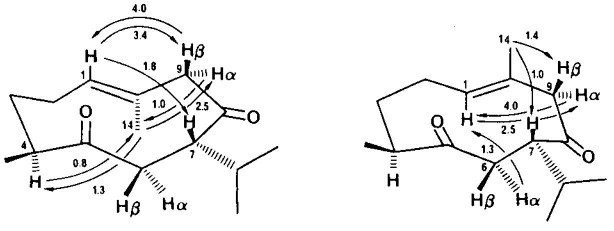


Fig 1. The Cd Spectrum of Curcumol 1.

A further evidence supporting the 7*S*-configuration of **1** was obtained as follows. The ketone **3** obtained by hydrogenation of **1** showed an intramolecular hydrogen bonding (OH··· O = C) at 3590 cm^{-1} in the ir spectrum, being in accord with the rigid conformation **3a**. The cd spectrum of **3** showed a negative Cotton effect, $[\theta]^{20}_{293}$ −3713 (dioxane). Application of the octant rule to **3a** led to the 7*S*-configuration of **3** and **1** [4].

Curdione (4) and Its One-Step Conversion into Curcumol (1).

Curdione (**4**) is a sesquiterpene isolated from *C. zedoaria* Roscoe [6] and *C. aromatica* Salisb [7]. Recently, Inayama *et al.* [8] reported that **4** (4*S*,7*S*) adopts the conformation **4a** in the solid state by X-ray analysis. They also showed the existence of two main conformations **4a** and **4b** in solution at −70° by variable-temperature ^{1}H nmr data. On the other hand, the co-existence of **4a** and **4b** was also observed by our nOe experiments at ambient temperature (Figure 2).



4a 4b

Fig. 2. Two Conformations of 4 and Their NOe Data (%).

The protons and carbons in **4** were completely assigned by the same way as employed for **1** (Table III). However, the ^{1}H nmr spectrum of **4** at ambient temperature corresponds to that of the equilibrating species between two conformations [8]. Irradiation of 1-H afforded nOe's at 7-H, 9β-H (**4a**) and 9α-H (**4b**). An nOe's was observed between 1-H and 6α-H (**4b**). Also, nOe's were observed on 4-H and 9α-H (**4a**), and 7-H and 9β-H (**4b**) on saturation of 14-H_3 (Me).

Table I

NMR Data for Curcumol (**1**) [a]

	Carbon	Correlated proton [b]		
No	δ c	One-bond [d]	Long-range	^{1}H-^{1}H [c]
1	54.44 d	1-H 2.165 dd (11.5, 9.0)	14-H_A, 14-H_B	2-H_2
2	28.20 t	2-H_2 1.700 m	1-H, 3α-H, 3β-H, 14-H_A, 14-H_B	1-H, 3α-H, 3β-H,
3	30.87	3α-H 1.480 m	15-H_3	2-H_2, 3β-H, 4-H
		3β-H 1.930 m		2-H_2, 3α-H, 4-H
4	39.35 d	4-H 1.860 m	3αH, 3β-H, 15-H_3	3α-H, 3β-H, 15-H_3
5	88.08 s		2-H_2, 3β-H, 6α-H, 6β-H, 15-H_3	
6	34.66 t	6α-H 1.165 dd (12.5, 6.5)	7-H	6β-H, 7-H
		6β-H 2.125 t (12.5)		6α-H, 7-H
7	56.27 d	7-H 1.450 m	6α-H, 6β-H, 9α-H, 9β-H, 12-H_3, 13-H_3, 8-OH	6α-H, 6β-H, 11-H
8	104.50 s		6β-H, 7-H, 9α-H, 9β-H, 8-OH	
9	38.78 t	9α-H 2.556 d (15.0)	14-H_A, 14-H_B	14-H_A, 14-H_B
		9β-H 2.513 dt (15.0, 1.0)		
10	144.70 s		9α-H, 9β-H	
11	28.68 d	11-H 1.660 m	6α-H, 6β-H, 7-H, 12H_3, 13-H_3	7-H, 12-H_3, 13-H_3
12	21.45 q	12-H_3 1.000 d (6.5)		11-H
13	23.04 q	13-H_3 0.854 d (6.5)	7-H	11-H
14	112.85 t	14-H_A 4.858 s	9α-H, 9β-H	9β-H
		14-H_B 4.862 s		9β-H
15	12.34 q	15-H_3 0.990 d (6.5)	3α-H	4-H
		8-OH, 2.725 s [e]		

[a] The spectra were taken on a Varian XL-400 (^{1}H, 400 MHz; ^{13}C, 100.6 MHz) in chloroform-d; ppm. [b] These data were obtained by ^{1}H-^{13}C COSY experiments. [c] These data were obtained by ^{1}H-^{1}H COSY experiments. [d] Figures in parentheses are coupling constants (J_{HH}, Hz). [e] This proton was exchangeable with deuterium oxide.

Pyrolysis of **4** gave **1** in quantitative yield [9], and its spectroscopic (uv, cd, ir, ^{1}H and ^{13}C nmr) data as well as melting point were perfectly the same as those of natural curcumol. This result showed that the ring closure reaction proceeds without epimerization at any asymmetric center in **4**. It seems probably that such a quantitative, stereospecific reaction proceeded *via* six-membered ring transition state **5**, which was developed from the ene-reaction [10] of **4b**, by following intramolecular hemiacetalization of the resulting ketone **6** [2] to afford **1**.

Table II

NOe Data for Curcumol (**1**)

Irradiated proton	Observed proton (nOe %)		
1-H	2-H_2 (8%),	3α-H (4%),	9α-H (2%)
4-H	1-H (5%),	3α-H (5%),	6β-H (3%)
6α-H	1-H (3%),	6β-H (17%)	
6β-H	6α-H (10%),	7-H (3%),	13-H_3 (3%)
12-H_3	1-H (6%), 11-H (11%)	8-OH (3%),	9α-H (3%),
13-H_3	1-H (1%), 7-H (5%),	6α-H (1%) 11-H (4%)	6β-H (2%),
15-H_3	3β-H (15%),	6β-H (6%)	

Table III

NMR Data for Curdione (**4**) [a]

	Carbon	Correlated proton [b]		
No	δ c	One-bond [d]	Long-range	^{1}H-^{1}H [c]
1	131.50 d	1-H 5.140 m	3-H_A, 14-H_3	2-H_2, 14-H_3
2	26.34 t	2-H_2 2.100 m		1-H, 3-H_A, 14-H_3
3	33.97 t	3-H_A 1.560 m	15-H_3	2-H_2, 3-H_B, 4-H
		3-H_B 2.090 m		3-H_A, 4-H
4	46.70 d	4-H 2.310 m	3-H_A, 15-H_3	3-H_A, 3-H_B, 15-H_3
5	214.26 s			
6	44.14 t	6α-H 2.674 dd (16.5, 8.5)	7-H	6β-H, 7-H
		6β-H 2.377 dd (16.5, 2.0)		6α-H, 7-H
7	53.54 d	7-H 2.828 dt (2.0, 8.5)	12-H_3, 13-H_3	6α-H, 6β-H, 11-H
8	211.00 s		6α-H, 6β-H, 7-H, 9α-H, 9β-H	
9	55.76 t	9α-H 2.917 d (11.0)	14-H_3	9β-H, 14-H_3
		9β-H 3.040 d (11.0)		9α-H
10	129.84 s			
11	29.90 d	11-H 1.850 m	6α-H, 6β-H, 7-H, 12-H_3, 13-H_3	7-H, 12-H_3, 13-H_3
12	19.78 q	12-H_3 0.930 d (7.0)	7-H, 13-H_3	11-H
13	21.04 q	13-H_3 0.863 d (6.5)	7-H, 12-H_3	11-H
14	16.48 q	14-H_3 1.630 s	1-H, 9α-H, 9β-H	1-H, 2-H_2, 9α-H
15	18.46 d	15-H_3 0.960 q (7.0)	3-H_A	4-H

[a] The spectra were taken on a Varian XL-400 (^{1}H, 400 MHz; ^{13}C, 100.6 MHz) in chloroform-d; ppm. [b] These data were obtained by ^{1}H-^{13}C COSY experiments. [c] These data were obtained by ^{1}H-^{1}H COSY experiments. [d] Figures in parentheses are coupling constants (J_{HH}, Hz).

EXPERIMENTAL

Melting points were determined on a micro hot-stage apparatus and are uncorrected. Specific rotations were taken on a JASCO DPI-181 polarimeter. Spectra were recorded on the following spectrometers: uv, Hitachi EPS-2U; cd, JASCO J-20 and J-600; ir, Hitachi 260-30; ^{1}H nmr, Varian VXR-300 (300 MHz) and XL-400 (400 MHz); ^{13}C nmr, Varian XL-400 at 100.6 MHz; ms, JEOL JMS DX-300; elemental analysis, Perkin-Elmer 240B. For the nOe spectra (400 MHz), the degassed solution was used. All nmr spectra were taken in chloroform-d solution at prove temperature, 20°, using a 5 mm tube.

H,H-COSY: ^{1}H single probe; 5 mm tube; relaxation time 1s; 90° (^{1}H) = 15 μs; 90° mixing pulse; $F_1 = F_2 = 1775$ Hz; data matrix 1024 x 128; 16 scans during 128 time increments (zero filling in F_1); 2 dummy scans; spectra were symmetrized.

H,C-COSY: ^{13}C, 30 ~ 105 MHz probe; 5 mm tube; relaxation time 1s; 90° (^{13}C) = 9.7 μs; $F_1 = 1736$ Hz, $F_2 = 13986$ Hz for one-bond correlation; $F_1 = 1736$ Hz, $F_2 = 14164$ Hz for long-range correlation; data matrix: 2048 x 64 for one-bond correlation, 2048 x 80 for long-range correlation; 16 scans during 64 time increments for one-bond correlation; 512 scans during 80 time increments for long-range correlation (zero filling in F_1); 2 dummy scans.

The nOe spectra were recorded by means of nOe difference techniques. The pre-irradiation time of each resonance was 3 seconds. The irradiation data sets were interleaved to cancel drift and changing magnet homogenity. These spectra were transformed by the difference between two free induction decays.

Properties of Curcumol (**1**).

This compound is colorless needles of mp 140-141° (ethanol), 147-148°; (ethyl acetate), Rƒ 0.30 (silica gel, chloroform), 0.51 (silica gel, petroleum ether-ethyl acetate = 85:15, v/v); specific rotations $[\alpha]^{26}$ (nm): −32.5° (589), −34.3° (577), −39.6° (546), −62.6° (435), −84.9° (365) (c = 0.53, chloroform); cd: $[\theta]^{25}$ (nm) 0 (221), +19100 (202), 0 (191) (c = 5.0 x 10^{-4}, methanol); ir (potassium bromide): cm^{-1} 3455 (OH), 1645 (C=C); ms: m/z M^+, 236.1764 (M, 236.1775), [lit [2], mp 141-142° (ethyl acetate); $[\alpha]_{589}$ −40.8° (c = 6.7, chloroform)].

Anal. Calcd. for $C_{15}H_{24}O_2$: C, 76.23; H, 10.23. Found: C, 76.09; H, 10.34.

Properties of Curdione (**4**).

This compound is colorless needles of mp 51-52° (hexane), Rƒ 0.42 (silica gel, hexane-ethyl acetate = 10:1, v/v); specific rotations $[\alpha]^{26}$ (nm): +263.3° (589), +280.6° (577), +333.7° (546), +764.9° (435), +2110.9° (365) (c = 0.99, chloroform); uv (methanol): λ max (ε) 298 (269), 213 (sh) (2966); cd: $[\theta]^{25}$ (nm) 0 (347), +8000 (318), +7333 (313), +7500 (310), +4000 (sh) (300), 0 (288), −1000 (276), 0 (251), +23400 (222), 0 (204), −38200 (192) (c = 5.0 x 10^{-4}, methanol); ir (potassium bromide): cm^{-1} 1705 (C=O), 1670 (C=C); ms: m/z M^+, 236.1770 (M, 236.1775); [lit [6], mp 61.5-62°; $[\alpha]_{589}$ +25.6° (chloroform)].

Anal. Calcd. for $C_{15}H_{24}O_2$: C, 76.23; H, 10.23. Found: C, 76.04; H, 10.29.

Ozonolysis of Curcumol (**1**).

A solution of **1** (8.6 mg) in dichloromethane (10 ml) was ozonized in the usual way under dry ice-acetone cooling until **1** disappeared (*ca.* 1 hour). After addition of dimethyl sulfide (2 ml), the mixture was stirred at ambient temperature for additional 1 hour. Work-up of the reaction mixture, followed by preparative tlc (silica gel, chloroform-methanol = 30:1, v/v) of the product, gave **2** (6.3 mg, 73%) as a colorless oil, R*f* 0.43 (silica gel, chloroform-methanol = 20:1, v/v); specific rotations $[\alpha]^{18}$ (nm): −53.1° (589), −53.8° (577), −63.1° (546), −120.6° (435), −215.0° (365) (c = 0.32, chloroform); uv (methanol): λ max (ϵ) 258 (188); cd: $[\theta]^{20}$ (nm) 0 (316), −1430 (292), 0 (234) (c = 8.97×10^{-4}, dioxane); ir (carbon tetrachloride): cm^{-1} 3590, 3400 (OH), 1710 (C=O); ^1H nmr: (300 MHz) δ 0.90, 0.99, 1.05 (each 3H, d, J = 6.5 Hz, Me x 3), 1.30 (1H, dd, J = 13.0, 6.5 Hz), 1.42 (1H, m), 1.54-1.67 (2H, m), 1.74-2.06 (4H, m), 2.31 (1H, t, J = 10.0 Hz), 2.31 (1H, t, J = 12.5 Hz), 2.66 (1H, dd, J = 16.5, 0.5 Hz), 2.77 (1H, dd, J = 16.5, 1.0 Hz), 2.81 (1H, s, 8-OH); ms: Calcd. for $C_{14}H_{22}O_3$: M, 238.1568. Found: m/z M^+, 238.1566. [lit [3], $[\alpha]^{30}_{589}$ −62.76° (c = 0.813, chloroform), $[\theta]^{25}_{294}$ −1423 (c = 0.01, dioxane)].

Hydrogenation of Curcumol (**1**).

A mixture of **1** (12.4 mg) and 5% Pd-C (6.0 mg) in methanol (10 ml) was stirred with hydrogen under atmospheric pressure at ambient temperature for 1 hour. Work-up of the reaction mixture, followed by preparative tlc (silica gel, benzene-ethyl acetate = 20:1, v/v) of the product gave **3** (3.6 mg, 29%) as a colorless oil, R*f* 0.22 (silica gel, benzene-ethyl acetate = 10:1, v/v); specific rotations $[\alpha]^{18}$ (nm): −52.9° (589), −40.0° (577), −52.9° (546), −131.8° (435), −328.2° (365) (c = 0.17, chloroform); uv (methanol): λ max (ϵ) 267 (206), 222 (806); cd: $[\theta]^{20}$ (nm) 0 (330), −3713 (293), 0 (240) (c = 7.7×10^{-4}, dioxane); ir (chloroform): cm^{-1} (ϵ) 3600 (OH), 1690 (C=O); 3610 (22.6) (free OH), 3590 (25.9) (bonded OH) (c = 7.9×10^{-4}, carbon tetrachloride); ^1H nmr: (300 MHz) δ 0.89, 0.91, 0.96, 0.99 (each 3H, d, J = 6.5 Hz, Me x 4), 1.25-1.43 (4H, m), 1.36 (1H, dd, J = 14.5, 11.5 Hz), 1.49-1.68 (3H, m), 1.72-1.86 (3H, m), 2.12 (1H, dd, J = 14.0, 6.0 Hz), 2.23-2.33 (1H, m), 2.44 (1H, t, J = 11.0 Hz); ms: Calcd. for $C_{15}H_{26}O_2$: M, 238.1931; Found: m/z M^+, 238.1934, [lit [2], $[\alpha]_{589}$ −94.7° (c = 4.9, chloroform)].

Pyrolysis of Curdione (**4**) to Curcumol (**1**).

A solution of **4** (200 mg) in ethanol (20 ml) was heated in a sealed tube at 180° for 5 hours. After cooling, the reaction mixture was concentrated to give **1** (200 mg, quantitative) as colorless needles of mp 140-141° (ethanol), 146-148° (ethyl acetate), R*f* 0.51 (silica gel, petroleum ether-ethyl acetate = 85:15, v/v). Mixed mp with natural curcumol was not depressed (141-142°); specific rotations $[\alpha]^{26}$ (nm): −35.8° (589), −36.7° (577), −49.9° (546), −67.8° (435), −88.9° (365) (c = 0.72, chloroform). Its cd, ir, ^1H and ^{13}C nmr spectra were superimposable on those of natural curcumol; ms: m/z M^+, 236.1776 (M, 236.1776).

Anal. Calcd. for $C_{15}H_{24}O_2$: C, 76.23; H, 10.23. Found: C, 75.90; H, 10.34.

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