X-Ray Crystallographic Analysis of Methyl (1*S*,2*R*,5*R*,6*S*,7*R*)-5,6-Dimethyl-2-(ω-camphanoyloxy)bicyclo[4.3.0]nonane-7-carboxylate. Revision of the Absolute Configurations of the Liverwort Sesquiterpenoids (−)-Chiloscyphone and (+)-Chiloscypholone

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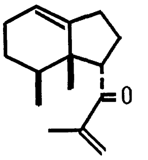
Synopsis. The X-ray analysis of the title compound has been carried out to give unambiguous assignment of the absolute configurations of the liverwort sesquiterpenoids (−)-chiloscyphone and (+)-chiloscypholone, each for which the enantiomerically opposite configurations had been assigned in the previous report.

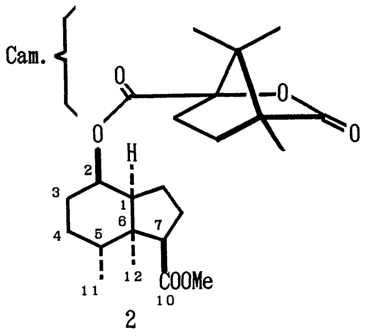
Determination of the absolute structure of the terpenoids isolated from the liverworts is a matter of interest, since it is closely related to their biological activities. In the previous work,[1] the absolute structures of **1** and **6** were elucidated on the basis of the analysis of the CD spectra of the synthetic intermediates in the total synthesis of **1**. In the present work, the absolute configuration of the title compound (**2**), one of the intermediates in the total synthesis of **1**,[1] was determined by X-ray analysis. The results gave the revision of our previous assignment of the absolute configurations of **1** and **6**.

Among the four ω-camphanic esters prepared,[1] **2**, $[\alpha]_D$ −1.4° (*c* 4.9 $CHCl_3$); mp 159—160 °C, was nicely recrystallized from chloroform–methanol, whose X-ray analysis has been carried out. The final atomic coordinates are listed in the Table 1.[2] Perspective view of the molecule is given in Fig. 1. This clearly shows that **2** has 1*S*, 2*R*, 5*R*, 6*S*, 7*R* configurations, since the absolute configurations of the camphanic ester part are known. That is, the absolute configuration of **2** is expressed as in the structure formula. This figure also shows that the conformation of the six-membered ring of the hydrindan system is chair and that the hydrindan system adopts nonsteroidal conformation.

In the total synthesis of **1**, we used the diastereomeric ω-camphanic ester **3** ($[\alpha]_D$ −7.8°), whose absolute configurations were clear, because both **2** and **3** were prepared from the corresponding alcohol (±)-**4** by camphanoylation and HPLC separation. The alcohol



(−)- Chiloscyphone (1)



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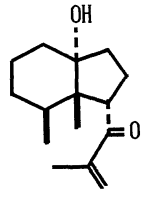

(+)-Chiloscypholone (6)

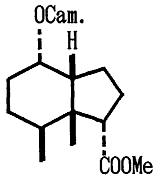

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Table 1. Non-Hydrogen Positional and Isotropic Displacement Parameters (Å²) for **2**, with esd's in Parentheses

	x/a	y/b	z/c	U_{eq}
C(1)	0.4083(2)	0.1998(5)	0.2287(2)	0.0406(6)
C(2)	0.4660(2)	0.07300	0.3145(2)	0.0445(7)
C(3)	0.4818(2)	−0.1189(5)	0.2669(3)	0.0520(8)
C(4)	0.3834(2)	−0.2041(5)	0.2231(3)	0.0534(8)
C(5)	0.3238(2)	−0.0854(5)	0.1326(2)	0.0427(7)
C(6)	0.3089(2)	0.1163(5)	0.1767(2)	0.0374(6)
C(7)	0.2855(2)	0.2563(5)	0.0734(2)	0.0449(7)
C(8)	0.3854(2)	0.2993(6)	0.0242(3)	0.0575(8)
C(9)	0.4652(2)	0.2579(5)	0.1221(3)	0.0528(8)
C(10)	0.2091(2)	0.1971(5)	−0.0228(2)	0.0517(7)
C(11)	0.2272(3)	−0.1895(6)	0.0968(3)	0.0648(9)
C(12)	0.2292(2)	0.1249(6)	0.2658(3)	0.0579(8)
C(13)	0.0392(3)	0.1728(9)	−0.0791(5)	0.110(1)
C(14)	0.7169(2)	0.2044(5)	0.4335(2)	0.0402(6)
C(15)	0.7257(2)	0.4109(5)	0.4031(3)	0.0464(7)
C(16)	0.8369(2)	0.4292(5)	0.3854(3)	0.0489(7)
C(17)	0.8778(2)	0.2274(5)	0.4035(2)	0.0424(7)
C(18)	0.8683(2)	0.1964(5)	0.5330(2)	0.0479(7)
C(19)	0.7889(2)	0.1074(5)	0.3524(2)	0.0383(6)
C(20)	0.6152(2)	0.1194(5)	0.4383(2)	0.0473(7)
C(21)	0.9797(2)	0.1933(6)	0.3613(3)	0.0619(8)
C(22)	0.7649(2)	0.1357(5)	0.2208(2)	0.0502(7)
C(23)	0.8018(3)	−0.1000(5)	0.3789(3)	0.0576(8)
O(1)	0.5621(1)	0.1650(4)	0.3397(2)	0.0502(5)
O(2)	0.2269(2)	0.1292(5)	−0.1144(2)	0.0727(7)
O(3)	0.1169(2)	0.2318(5)	0.0067(2)	0.0801(8)
O(4)	0.9299(2)	0.1875(5)	0.6137(2)	0.0684(7)
O(5)	0.5881(2)	0.0227(5)	0.5150(2)	0.0749(7)
O(6)	0.7694(1)	0.1829(4)	0.5495(1)	0.0487(5)

a) $U_{\text{eq}}=\frac{1}{3}\sum_i\sum_j U_{ij}\,a_i^*a_j^*\boldsymbol{a}_i\boldsymbol{a}_j$.

(+)-**4** was derived from **3** by alkaline treatment.[1] The sign of the specific rotation of the corresponding ketone **5** was (−) and the sign of the Cotton effect was (−). The back octant of (−)-**5** shown in Fig. 2 suggests that the expected sign of the Cotton effect should be (−), which was erroneously assigned previously.[1] Since the results of the X-ray analysis of **2** are unambiguous and natural (−)-chiloscyphone (**1**) had been synthesized from the diastereomeric isomer **3**,[1] the absolute configuration of (−)-**1** as well as (+)-chiloscypholone (**6**), which was converted to (−)-**1**,[1] should be formulated as depicted in the scheme.

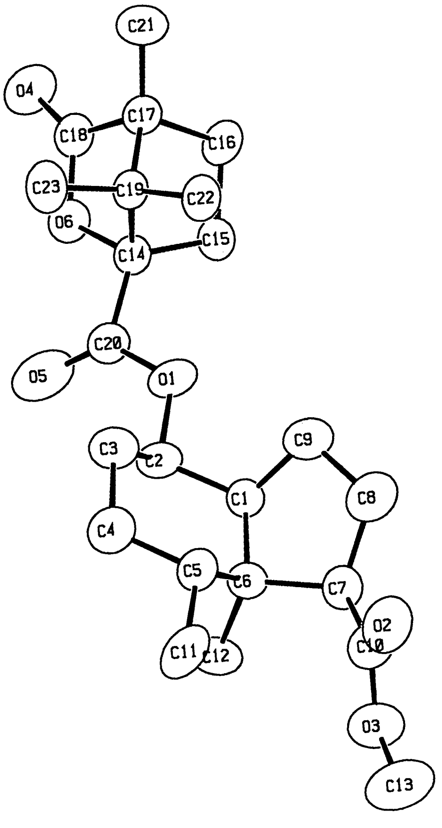

Fig. 1. Computer generated perspective view of **2**.

Experimental

General. See Ref. 1.

Single-Crystal X-Ray Structure Analysis. Crystals of **2** were recrystallized from chloroform–methanol. A truncated rectangular prism of approximately 0.5×0.5×0.5 mm was chosen for X-ray measurements. The crystals are monoclinic, space group $P2_1$ (No. 4), with a=13.516 (1), b=7.1924 (7), c=11.398 (1) Å, β=93.94 (1)°, V=1105.4 (2) Å^3, and d_{calcd}=1.221 g cm^{-3} for Z=2 ($C_{23}H_{34}O_6$, M=406.52). Intensity data were measured at 298 K on a Rigaku AFC-5 diffractometer with graphite monochromated Mo $K\alpha$ radiation (λ=0.71073 Å). The cell dimensions were obtained from the least-squares refinement of 50θ values in the range of $25<2\theta<40°$. The data were collected using the ω–2θ scan technique at an ω rate of 3.0° min^{-1} with a 2θ range from 3.0—60.0°. Data having $-19\leqslant h\leqslant 19$, $-10\leqslant k\leqslant 0$, $0\leqslant l\leqslant 16$ were measured. Three reflections (200, 040, 004) were remeasured every 100 reflections to monitor instrument and crystal stability, and the intensity monotonically decreased 17% during the measurement. All the intensity data were empirically corrected on the basis of the intensity variation of the three standard reflections using UNICS3.[3] Of 2928 reflections with $F_o\geqslant 3\sigma(F_o)$, 2491 were unique, with R_{int}=0.0071 from averaging symmetry-equivalent reflections. The data were corrected for Lp effects, but not for absorption.

The structure was solved by direct methods with SHELXS86[4] and refined by full-matrix least squares with SHELX76.[5] The number of the parameters refined was 397. The non-H atoms were refined with anisotropic displacement parameters. All of the H-atoms were initially calculated in idealized positions but were refined under the C–H bond length constraint during the final refinement cycles. The function $\Sigma(|F_o|-|F_c|)^2$ was optimized, where $w=[\sigma^2(F_o)+0.0004(F_o)^2]^{-1}$. In the final least-squares refinement, R=0.045, R_w=0.051, S=1.544, and $(\Delta/\sigma)_{\max}$=0.396. The maximum and the minimum height in the final difference Fourier synthesis were 0.15 and −0.26 eÅ^{-3}, respectively. Atomic scattering factors were taken from International Tables for X-Ray Crystallography.[6] Calculations of the geometrical parameters and drawing of the ORTEP diagrams were performed using XTAL3.0 software.[7]

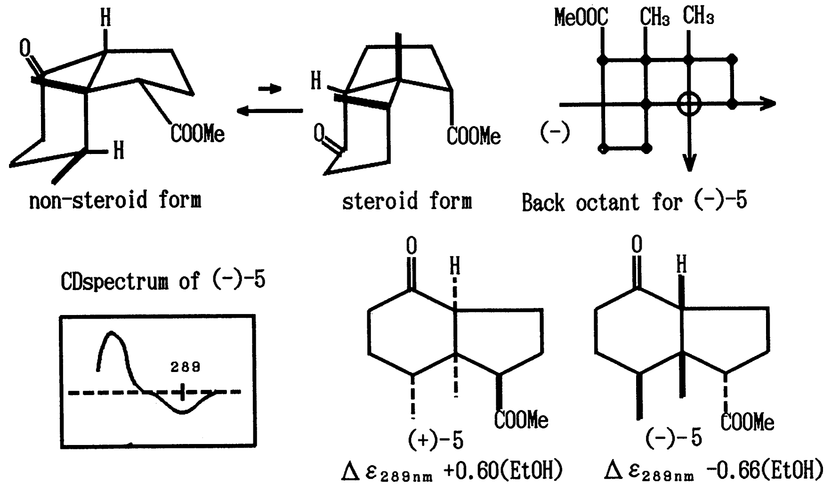

Fig. 2. The CD spectrum and back octant for (−)-(5).

References

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