Pergamon

Tetrahedron Letters, Vol. 37, No. 27, pp. 4745-4748, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)00956-2

(+)-Cavicularin : A Novel Optically Active Cyclic Bibenzyl-Dihydrophenanthrene Derivative from the Liverwort *Cavicularia densa* Steph.

Masao Toyota, Tatsuhiko Yoshida, Yukiko Kan, Shigeru Takaoka, and Yoshinori Asakawa *

Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Yamashiro-cho, Tokushima 770, Japan

Abstract : From the methanolic extract of the liverwort *Cavicularia densa* a novel phenolic secondary metabolite, (+)-cavicularin (**1**) has been isolated. The structure was determined by extensive high field (600MHz) 2D-NMR spectra and it was confirmed by an X-ray crystallographic analysis. It was shown to be a cyclic bibenzyl-dihydrophenanthrene derivative, having a highly strained structure. The unique structure of **1**, $[\alpha]_D^{21}$ +168.2° (*c* 0.25, MeOH) possesses both planar and axial chirality. This is the first example of the isolation of such a compound from nature. Copyright © 1996 Elsevier Science Ltd

We are continuing to study the chemical constituents of liverworts (Hepaticae) which are widely distributed in the world.[1] Some species of liverworts are rich sources of both terpenoids and aromatic compounds with biological activities. We have reported the distribution of a number of new terpenoids and aromatic compounds in more than 200 species of the liverwort.[1] The Hepaticae occasionally produce their own peculiar bis(bibenzyl) derivatives.

Our previous work resulted in the isolation of cyclic bis(bibenzyl) type marchantin A, possessing cytotoxic, 5-lipoxygenase and calmodulin inhibitory, and *d*-tubocurarine-like muscle relaxing activities from *Marchantia polymorpha*.[1] Further investigation of liverworts led to the isolation of riccardin A, showing cytotoxic, antimicrobial and antifungal activity from *Riccardia multifida*.[1, 2] These bis(bibenzyl) derivatives have not been found in higher plants, fungi or marine organisms.

In the course of the isolation of the biologically active substances from liverworts, we isolated a novel optically active cyclic bibenzyl-dihydrophenanthrene derivative, (+)-cavicularin (**1**) from the methanolic extract of *Cavicularia densa* Steph. (Blasiaceae), a species which has not yet been investigated phytochemically. Here, we wish to report on the isolation and structure elucidation of **1**.

The liverwort *C. densa* was collected on Mt. Ishizuchi, Ehime, in 1995. The liverwort was dried for 1 day and mechanically powdered. 5.1g of the ground material was extracted with 120ml of methanol for 4 months. The methanolic extract (302.3mg) was chromatographed on Sephadex LH-20 (MeOH) and further purified by preparative TLC (*n*-hexane - AcOEt = 1:1) to give (+)-cavicularin (**1**) (2.5mg). The compound **1** was obtained as a white powder, mp 244 - 246 °C. The EI mass spectrum exhibited a $[M]^+$ peak at *m/z* 422 (100) and significant fragment peaks (relative intensity) at *m/z* 331(41), and 211 (12). Molecular formula of **1** was established as $C_{28}H_{22}O_4$ by high resolution mass spectrometry. The UV spectrum (MeOH) showed strong absorption maxima at 315 (log ε=3.83), 285 (log ε=4.03) and 212 nm (log ε=4.43). The IR spectrum (KBr) displayed absorption bands at 3376 (OH), 2926, 2855 (C-H), 1580, 1505, 1441 cm^{-1} (benzenoid).

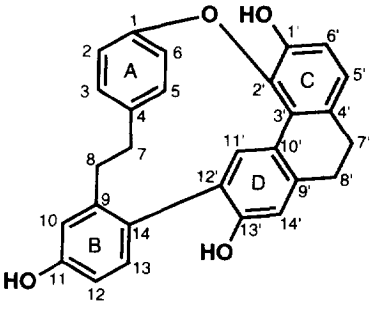


Chart 1.
Planar structure of **1**

Table 1. High-field (600MHz) NMR assignments (in $CDCl_3$) for (+)-cavicularin (**1**) [a]

Position no.	^1H (δ)	^{13}C (δ)	HMBC	NOESY
A-1		153.8	2-H, 3-H, 5-H, 6-H	
A-2	6.10 (dd, J = 8.6, 2.7)[d]	115.1	6-H	
A-3	6.46 (dd, J = 8.6, 2.2)[e]	127.8	5-H	8-H
A-4		135.0	2-H, 6-H	
A-5	6.15 (dd, J = 8.3, 2.2)[e]	130.0	3-H	7-H
A-6	6.71 (dd, J = 8.3, 2.7)[d]	117.8	2-H	
7	2.55 (ddd, J = 17.6, 13.4, 4.4) 2.96 (m)[b]	38.1	3-H, 5-H	5-H, 8-H, 10-H
8	2.28 (ddd, J = 17.6, 13.4, 4.4) 2.94 (m)[b]	37.4	10-H	3-H, 7-H
B-9		141.6	13-H	
B-10	6.88 (d, J = 2.7)	116.9	12-H	
B-11		155.5	13-H	
B-12	6.75 (dd, J = 8.3, 2.7)	114.7	10-H	
B-13	6.82 (d, J = 8.3)	131.6		11'-H
B-14		128.9	10-H, 12-H, 11'-H	
11-OH	4.88 (brs)			
C-1'		147.8	5'-H, 1'-OH	
C-2'		138.5	6'-H, 1'-OH	
C-3'		123.3	5'-H, 11'-H	
C-4'		131.7	6'-H	
C-5'	6.98 (d, J = 8.1)	123.0		7'-H
C-6'	6.94 (d, J = 8.1)	113.0	1'-OH	
1'-OH	6.12 (s)			
7'	2.66 (m)[c], 2.76 (m)	30.2	5'-H	5'-H, 8'-H
8'	2.66 (2H, m)[c]	30.5	14'-H	7'-H, 14'-H
D-9'		140.5	11'-H	
D-10'		124.0	14'-H	
D-11'	6.40 (s)	131.1		13-H
D-12'		124.0	13-H, 14'-H, 13'-OH	
D-13'		150.2	11'-H, 14'-H, 13'-OH	
D-14'	6.68 (s)	113.2	13'-OH	8'-H
13'-OH	4.75 (s)			

[a] Chemical shifts from TMS (multiplicity, J in Hz). [b, c] Overlapped signals.
[d, e] May be interchanged in each vertical column.

For further characterization of the compound, we have carried out extensive NMR studies. The 1D-NMR ^{1}H and ^{13}C and 2D-NMR employing ^{1}H-^{1}H-COSY, NOESY, HSQC, and HMBC spectra were obtained on a 600MHz spectrometer in $CDCl_3$ solutions (Table 1). The ^{1}H NMR spectrum indicated the presence of 11 protons on benzene rings at δ 6.10-6.98 ppm and four benzylic methylenes at δ 2.28-2.96 ppm (8H). The HMBC data supported the proposed structure **1**.

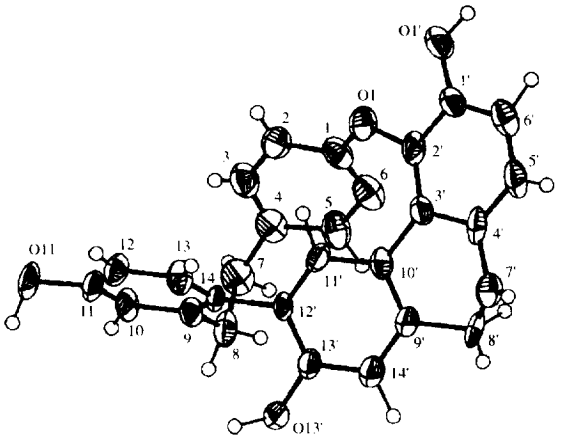


Figure 1.
ORTEP diagram of **1** (relative stereochemistry)

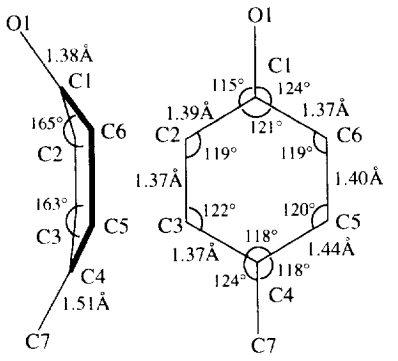
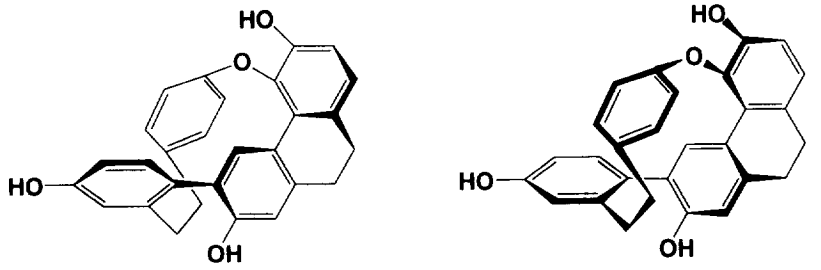


Figure 2. Diagram of the benzene ring (A) of **1** showing bond lengths, dihedral and inter-bond angles.



(1a) **(1b)**

Figure 3. Restricted absolute structures **1a** or **1b** for (+)-cavicularin

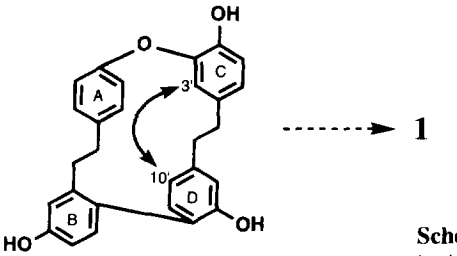
In order to confirm the proposed structure and to establish the overall stereochemistry of **1**, X-ray crystallographic analysis was performed on a crystal obtained from *n*-hexane - AcOEt (9:1) solution. An ORTEP diagram showing the relative stereochemistry and solid-state conformation is shown in Fig. 1.[3] It was revealed that the cyclic bibenzyl-dihydrophenanthrene skeleton has a highly strained structure and the benzene ring (A) was twisted (Fig. 2). Similar examples have been reported in the case of [2. 2] paracyclophane compounds.[4] The absolute structure of (+)-cavicularin (**1**) was restricted to **1a** or **1b** by X-ray crystallographic analysis (Fig. 3).

Although the structure of **1** has no chiral carbon center, its $[\alpha]_D^{21}$ showed +168.2° (*c* 0.25, MeOH) and the CD spectrum exhibited Cotton effects due to the $\pi \rightarrow \pi^*$ transition of the asymmetric aryls [λ_{ext} 312nm (Δε +4.6), 280 (+2.6), 255 (-2.6), 208 (+24.6) (*c* 2.5 x 10^{-5} g/ml, MeOH)]. This phenomenon suggested that **1**

possessed both planar and axial chirality.

A determination of the enantiomeric purity of (+)-cavicularin was performed by the ^{1}H NMR analysis of its (1*S*)-(-)-camphanyl triester.[5] The signals due to the enamtiomeric isomer were not detected by ^{1}H NMR spectroscopy.

C. densa might generate (+)-cavicularin (**1**) which is formed by intramolecular phenolic oxidative coupling between 3' and 10' position of riccardin C (**2**)[6] (Scheme 1) isolated from the same family (*Blasia pusilla*, Blasiaceae). On the other hand, *B. pusilla* produced riccardin C dimer pusilatins A-D[6] biosynthesized by intermolecular coupling between two molecules of **2**. These bibenzyl derivatives are significant chemical markers of the Blasiaceae.



(**2**)

⟶ **1**

Scheme 1. Possible biogenetic pathway of **1** by intramolecular phenolic oxidation of precursor **2**

Acknowledgments

We thank Dr. T. Hashimoto (TBU) for providing liverwort plant material and Dr. M. Mizutani (The Hattori Botanical Laboratory, Nichinan, Japan) for the identification of *C. densa*. Thanks are also due to Miss Y. Okamoto (TBU) for the measurements of mass spectra.

References and Notes

1. (a) Asakawa, Y. Chemical Constituents of Hepaticae in "*Progress in the Chemistry of Organic Natural Products*" (Herz, W.; Kirby, G. W.; Moore, R. E.; Steglich, W.; Tamm, Ch. eds.) **1995**, Vol. 65, P. 1, Springer, Wien. (b) Asakawa, Y. Biologically Active Terpenoids and Aromatic Compounds from Liverworts and the Inedible Mushroom *Cryptoporus volvatus*. in "*Bioactive Natural Products: Detection, Isolation, and Structural Determination*" (Colegate, S. M.; Molyneux, R. J. eds.) **1993**, P. 319, CRC Press, Florida.
2. Asakawa, Y.; Toyota, M.; Taira, Z.; Takemoto, T.; Kido, M. *J. Org. Chem.* **1983**, *48*, 2164-2167.
3. The crystal data for **1** are as follows : crystal dimensions = 0.50 x 0.20 x 0.05 mm, orthorhombic, space group $P2_12_12_1$ (no.19), a = 19.796 (5)Å, b = 21.151 (5)Å, c = 11.442 (4)Å, V = 4791 (2)Å^3, Z = 8, $F(000)$ = 1776, D_{calc} = 1.17g cm^{-3}, μ (Cu Kα) = 5.50cm^{-1}, Final R and R_w were 0.091 and 0.083 for 3398 reflections with $I > 3\sigma(I)$. The structure was solved by direct method (Monte-Carlo Multan) and refined by full-matrix least-squares techniques. The final R value did not decrease to less than 0.091, since the crystals contain solvent of crystallization, which is probably *n*-hexane, although disorder within the solvent region makes it difficult to be absolutely certain about the composition of the solvent. Diffraction data were obtained using a Mac Science MXC18 diffractiotometer at room temperature. The supplementary materials have been deposited at the Cambridge Crystallographic Data Center.
4. (a) Brown, C. J.; Farthing, A. C. *Nature* **1949**, *164*, 915-916. (b) Brown, C. J. *J. Chem. Soc.* **1953**, 3265-3270.
5. Esterification of **1** (0.006 mmol) with excess (1*S*)-(-)-camphanic chloride / excess Et_3N / DMAP in CH_2Cl_2 (0.3 ml) solution at room temperature (3 days, y. 19.3%).
6. Hashimoto, T.; Yoshida, T.; Kan, Y.; Takaoka, S.; Tori, M.; Asakawa, Y. *Tetrahedron Lett.* **1994**, *35*, 909-910.

(*Received in Japan* 11 *April* 1996; *revised* 16 *May* 1996; *accepted* 17 *May* 1996)