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THE ABSOLUTE STEREOSTRUCTURE OF DIONCOPHYLLINE A BY ANOMALOUS X-RAY DISPERSION OF A 5-BROMO DERIVATIVE*

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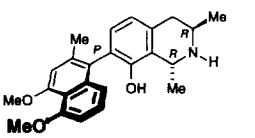
Key Word Index—*Triphyophyllum peltatum*; Dioncophyllaceae; dioncophylline A; naphthylisoquinoline alkaloids; absolute configuration; X-ray crystallography.

Abstract—The absolute configuration of the naphthylisoquinoline alkaloid dioncophylline A was determined by anomalous X-ray dispersion crystal structure analysis of its bisbenzylated bromo derivative.

INTRODUCTION

Among the rapidly growing young class of naphthylisoquinoline alkaloids [2], dioncophylline A (**1**) occupies an outstanding role, given its occurrence as a main alkaloid not only in the carnivorous tropical liana *Triphyophyllum peltatum* (Dioncophyllaceae) [3], but also in taxonomically related *Ancistrocladus* species (Ancistrocladaceae) [2, 4, 5]. Moreover, it exhibits fungicidal [6], insect growth retarding, and antifeedent [7], as well as molluscicidal [8], activities. For this unusual isoquinoline alkaloid (previously 'triphyophylline'), initially the gross structure **2** was proposed [9], with the correct constitution and relative configuration, but with the incorrect absolute *S,S*-configuration at the two stereocenters, C-1 and C-3, and with complete neglect of axial chirality.

We have recently reinvestigated dioncophylline A, by applying a broad variety of spectroscopic, computational and chemical methods [3, 10–15], including a 'normal' X-ray structure analysis [16] and a stereoselective total synthesis [10, 17], and have thus revised its structure as **1**, with 1*R*,3*R*,7*P*-configuration [10]. Because of the importance of dioncophylline A, the availability of yet another independent method for the further confirmation of the absolute configuration of this first fully assigned Dioncophyllaceae alkaloid seemed highly desirable. In this paper, we describe the rigorous additional proof of the stereostructure of dioncophylline A as **1** by anomalous X-ray dispersion, which again perfectly confirms the relative and absolute configuration of this well-known natural product as established previously.



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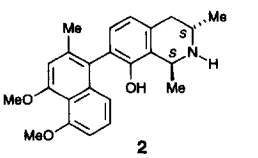

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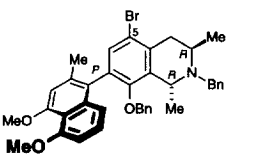

3

RESULTS AND DISCUSSION

As an appropriate derivative of the natural product dioncophylline A (**1**), which, itself, does not dispose of a 'heavy atom' substituent, we chose its 5-bromo derivative **3**, which is easily available by regioselective bromination of **1** and subsequent *O*- and *N*-benzylation reaction [18]. Suitable crystals of **3** were obtained by crystallization from methanol, giving colourless plates.

The crystal structure analysis [Fig. 1(a)] fully confirms the constitution of **3** and thus of the natural product dioncophylline A (**1**), as well as its relative configuration—the *trans*-orientation of the two methyl groups at C-1 and at C-3 and the relative axial configuration with the methyl group on the naph-

* Part 86 in the series 'Acetogenic Isoquinoline Alkaloids'. For Part 85, see ref. [1].

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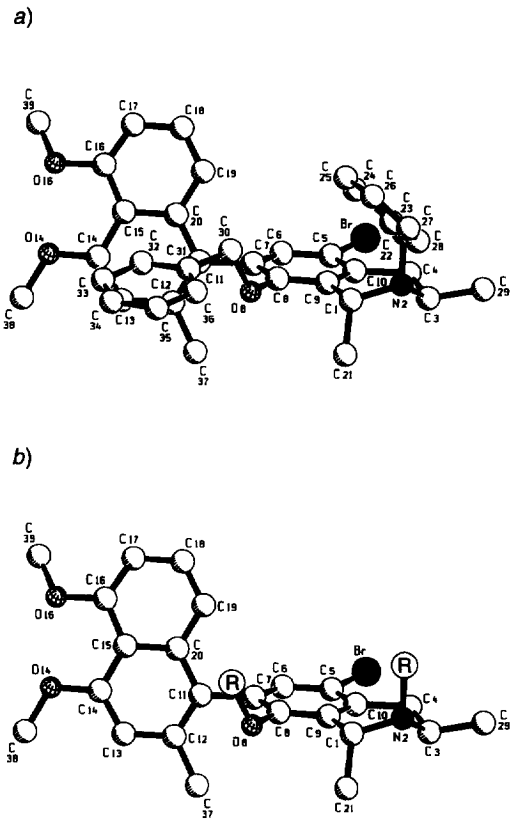

Fig. 1. (a) Perspective drawing of the full absolute structure of **3**, with the hydrogen atoms omitted. (b) Perspective drawing of **3** with the benzyl residues reduced to '*R*' for reasons of clarity in favour of the parent alkaloid structure.

thalene being located on the same side of the molecule as the methyl group at C-1 [Fig. 1(b)]. As for related *N*-benzylated *trans*-configured 1,3-dimethyl-tetrahydroisoquinoline derivatives [10, 19], the *N*-substituent is orientated *trans* to the axial methyl group at C-1, and *cis* to the equatorial methyl group at C-3, thus minimizing steric interaction by displaying a gauche and a more favorable antiperiplanar array, instead of two unfavourable gauche interactions if the *N*-substituent was equatorial. More importantly, the analysis reveals that the absolute configuration of dioncophylline A fully corresponds to the one previously established [10], *viz.* 1*R*,3*R*,7*P*, as presented by the structural formula **1**. This result underlines the reliability of the broad array of methods now available for the unequivocal structural elucidation of naphthylisoquinoline alkaloids.

EXPERIMENTAL

General. Compound **3** was prepd as described previously [18]. The X-ray data were obtained at room temp. on a Siemens P4 diffractometer using graphite monochromatized Mo*K*α radiation.

X-Ray analysis of compound **3**. Crystals suited for an X-ray structure analysis were obtained from MeOH. Crystals dimensions, 0.15 × 0.45 × 0.75 mm, $C_{38}H_{38}BrNO_3$, $M_r = 636.63$, monoclinic, $a = 10.026(2)$, $b = 8.750(2)$, $c = 18.870(4)$ Å, $\beta = 98.37(2)°$, $V = 1637.8(8)$ Å^3, space group $P2_1$ (#4), $Z = 2$, $D_c = 1.291$ g cm^{-3}, μ(Mo*K*α) = 12.9 cm^{-1}, F(000) = 664. A total of 8434 reflections (7527 unique within Friedel reflections, necessary for the determination of the absolute configuration; SHELXTL PLUS; *R*-factor test parameter according to ref. [20]: 1.01(2)) were collected using the ω scan technique within a 2θ range of 55°. The structure was solved by direct methods and refined by a full-matrix least-squares method using 5106 reflections [$I_0 > 3.0\sigma(I)$].

Table 1. Atomic parameters (× 10^4) and equivalent isotropic displacement parameters (pm^2 × 10^{-1}) of non-hydrogen atoms for compound **3**

Atom	*x*	*y*	*z*	Ueq
Br	222(1)	6424	2336(1)	96(1)
C(1)	−2352(5)	2201(5)	3720(2)	54(2)
N(2)	−1368(3)	2574(4)	4350(2)	59(1)
C(3)	−18(4)	2788(6)	4119(3)	67(2)
C(4)	14(5)	4090(6)	3607(3)	67(2)
C(5)	−1275(5)	5166(5)	2464(3)	65(2)
C(6)	−2395(5)	5262(5)	1950(3)	66(2)
C(7)	−3567(5)	4429(5)	2006(3)	59(2)
C(8)	−3490(4)	3455(5)	2591(2)	54(2)
O(8)	−4605(3)	2532(3)	2660(2)	56(1)
C(9)	−2355(4)	3309(5)	3110(2)	54(2)
C(10)	−1220(4)	4187(5)	3041(3)	58(2)
C(11)	−4753(4)	4532(5)	1433(2)	53(2)
C(12)	−5076(5)	3362(5)	975(2)	59(2)
C(13)	−6182(5)	3501(5)	422(3)	64(2)
C(14)	−6934(5)	4800(5)	331(2)	61(2)
O(14)	−8015(4)	4952(4)	−192(2)	87(2)
C(15)	−6634(5)	6095(5)	788(2)	59(2)
C(16)	−7292(5)	7536(6)	727(3)	75(2)
O(16)	−8281(4)	7721(5)	143(3)	99(2)
C(17)	−6939(6)	8664(6)	1218(3)	83(2)
C(18)	−5929(6)	8449(7)	1790(3)	85(2)
C(19)	−5238(5)	7130(6)	1859(3)	74(2)
C(20)	−5516(5)	5922(5)	1366(2)	59(2)
C(21)	−2197(5)	563(5)	3464(3)	64(2)
C(22)	−1812(5)	3913(5)	4714(3)	68(2)
C(23)	−2907(5)	3527(5)	5146(2)	59(2)
C(24)	−4132(6)	4308(6)	5031(3)	78(2)
C(25)	−5102(6)	4021(9)	5458(4)	95(3)
C(26)	−4891(7)	3004(8)	6003(4)	94(3)
C(27)	−3708(7)	2223(7)	6120(3)	91(3)
C(28)	−2713(5)	2499(7)	5692(3)	77(2)
C(29)	1086(5)	2965(7)	4770(3)	84(2)
C(30)	−5724(5)	3352(6)	2903(3)	68(2)
C(31)	−6983(4)	2439(5)	2685(2)	55(2)
C(32)	−7851(5)	2838(6)	2070(3)	73(2)
C(33)	−9024(5)	1977(8)	1883(3)	85(2)
C(34)	−9310(6)	783(8)	2292(3)	86(2)
C(35)	−8451(5)	384(6)	2871(3)	76(2)
C(36)	−7307(4)	1212(6)	3080(3)	64(2)
C(37)	−4291(5)	1900(5)	1017(3)	77(2)
C(38)	−8285(8)	3740(8)	−689(4)	127(3)
C(39)	−8596(8)	9213(8)	−83(5)	131(4)

The final refinement converged to $R = 0.060$ and $R_w = 0.052$. Atomic coordinates, bond lengths and angles, and thermal parameters may be obtained from the Fachinformationszentrum Karlsruhe, D-76344 Eggenstein–Leopoldshafen (Germany) on quoting the depository number CSD-405465.

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