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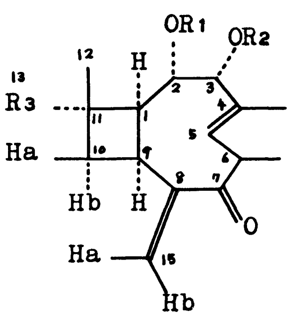
# STRUCTURES OF NAEMATOLIN AND NAEMATOLIN B, 1S,9S-RING-FUSED CARYOPHYLLANE SESQUITERPENOIDS

Kozo DOI,* Takao SHIBATA, Masataka NARA, Sei TSUBOYAMA,†
Tosio SAKURAI,† and Kaoru TSUBOYAMA†
Department of Chemistry, Faculty of Science, Hirosaki
University, Hirosaki-shi, Aomori 036
†The Institute of Physical and Chemical Research (Rikagaku
Kenkyusho), Wako-shi, Saitama 351

It is well known that naturally occurring caryophyllane sesquiterpenoids possess in general 1R,9S(trans)-ring juncture. However, it has been clarified that both of naematolin and naematolin B, microbial products, have 1S,9S(cis)-ring juncture in the caryophyllane skeleton.

Y.Ito *et al.*1) reported the isolation of naematolin from a liquid culture of mycelium of *Naematoloma fasciculare*(Nigakuritake in Japanese), although its structure was not deduced at that time. The authors reported, in the course of investigating metabolites of this fungus,2) the isolation and structural elucidation of two compounds. The first one (naematolin, 1), $C_{17}H_{24}O_5$,3) mp 144-145 °C, $[\alpha]_D^{22}$ -330°, afforded in a usual way an acetate (2), $C_{21}H_{28}O_7$, mp 134-135 °C, $[\alpha]_D^{22}$ -260°, which was identical with naematolin acetate1,4) by means of their mixed mp test and of the comparison of each $^1$H-NOE. The second one, that was designated as naematolin B (5, mp 122-123 °C, and $[\alpha]_D^{23}$ -352°), has a molecular formula of $C_{17}H_{24}O_6$, indicative of a hydroxynaematolin. We wish to describe herein the structures of naematolin (1) and naematolin B (5).



1: $R_1=R_2=H$, $R_3=CH_3$
2: $R_1=R_2=CH_3CO$, $R_3=CH_3$
3: $R_1=R_2=C_6H_5CO$, $R_3=CH_3$
4: $R_1=H$, $R_2=p\text{-}BrC_6H_4CO$, $R_3=CH_3$
5: $R_1=R_2=H$, $R_3=CH_2OH$

In order to elucidate the stereochemistry of 1, the following derivatives were prepared: naematolin dibenzoate (3), $C_{31}H_{32}O_7$, mp 146-147 °C, and naematolin mono *p*-bromobenzoate (4), $C_{24}H_{27}O_6Br$, mp 122-123 °C.

$^1$H- and $^{13}$C-NMR data of 2, 4, and 5 are cited in Table 1, wherein the assignments of each signal have been carried out using $^1$H spin-spin decoupling, 2D $^1$H-$^1$H COSY, INEPT, and 2D $^1$H-$^{13}$C COSY.5)

Table 1. $^{1}$H- and $^{13}$C-NMR of $\underline{2}$, $\underline{4}$, and $\underline{5}$

| No. of C | $\underline{2}$ | | $\underline{4}$ | $\underline{5}$ | |
|---|---|---|---|---|---|
| | $^{13}$C | $^{1}$H(J) | $^{1}$H(J) | $^{13}$C | $^{1}$H(J) |
| 1 | 44.9 d | 3.09 t(11) | 2.90 t(11) | 45.1 d | 3.12 t(11) |
| 2 | 70.8 d | 4.86 dd(12,2) | 3.89 dd(12,2) | 70.6 d | 3.55 dd(11,1.5) |
| 3 | 75.0 d | 5.23 d(2) | 5.23 d(2) | 78.1 d | 4.06 d(1.5) |
| 4 | 143.3 s | | | 148.6 s | |
| 5 | 117.8 d | 6.10 d(9) | 6.08 d(9) | 117.1 d | 6.32 d(9) |
| 6 | 71.0 d | 5.76 d(9) | 5.76 d(9) | 72.8 d | 5.82 d(9) |
| 7 | 195.2 s | | | 196.8 s | |
| 8 | 148.4 s | | | 151.0 s | |
| 9 | 35.1 d | 3.18 td(10,5) | 3.19 td(10,5) | 36.6 d | 3.31 td(11,5) |
| 10a | | 1.85 dd(12,5) | 1.88 dd(12,5) | | 1.69 dd(13,5) |
| 10 | 40.9 t | | | 36.8 t | |
| 10b | | 2.23 dd(12,10) | 2.23 dd(12,10) | | 2.24 dd(13,10) |
| 11 | 34.6 s | | | 40.5 s | |
| 12 | 23.3 q | 1.05 s | 1.27 s | 19.7 q | 1.30 s |
| 13 | 33.0 q | 1.22 s | 1.32 s | 73.3 t | 3.42 AB(2H,9.8) |
| 14 | 18.2 q | 1.67 br.s | 1.69 br.s | 19.3 q | 1.52 d(1.5) |
| 15a | | 5.80 s | 5.84 s | | 5.83 s |
| 15 | 127.3 t | | | 126.6 t | |
| 15b | | 6.56 s | 6.55 s | | 6.42 s |
| $\underline{\mathrm{CH_3}}\mathrm{CO}$ | 21.1 q | 2.01 s | 2.16 s | 21.1 q | 2.11 s |
| $\underline{\mathrm{CH_3}}\mathrm{CO}$ | 20.6 q | 2.17 s | | | |
| $\underline{\mathrm{CH_3}}\mathrm{CO}$ | 20.9 q | 2.19 s | | | |
| $\mathrm{CH_3}\underline{\mathrm{CO}}$ | 169.4 s | | | 170.5 s | |
| $\mathrm{CH_3}\underline{\mathrm{CO}}$ | 169.8 s | | | | |
| $\mathrm{CH_3}\underline{\mathrm{CO}}$ | 170.0 s | | | | |
| OH | | | 1.60 br.s(1H) | | 2.84 d(3H) |
| others | | | 7.66 d(2H,8.5)<br>7.95 d(2H,8.5) | | |

The spectra were taken on a JEOL JNM-GX400 in the each solvent($\underline{2}$ and $\underline{4}$: chloroform-d; $\underline{5}$: acetone-$d_6$).

It is evident from the above Table 1 that the geometry of 4-endocyclic double bond of $\underline{1}$ is trans based on the chemical shift of 14-methyl in $^{13}$C-NMR.$^{6)}$ In addition, p-bromobenzoyloxyl group in $\underline{4}$ and the third hydroxyl one in $\underline{5}$ must be attached to C(3) and C(13), respectively.

The circular dichroism spectrum$^{7)}$ of $\underline{3}$ showed that the first Cotton effect was negative($\Delta\epsilon_{241}$ -33.9) and the second one was positive($\Delta\epsilon_{220}$ +15.2), indicating that $\underline{3}$ has negative chirality in the light of the dibenzoate exciton chirality rule.$^{8)}$ From this fact, $\underline{1}$ possesses clearly the 2S,3R-glycol system.

In order to determine the stereochemistry of the additional chiral centers in 1 except for C(2) and C(3), NOE difference spectra of 2 were measured,9) and the results were summarized in Table 2. On irradiation at 12-H, NOEs were observed not only at 2-H but at 15-Ha, suggesting that both of C(1)-C(2) and C(8)-C(9) bondings are in a cis configuration, and accordingly the juncture between the four- and nine-membered rings is also cis. Furthermore, NOEs by the irradiations of 5- and 9-H vertify that the four protons at 1-, 5-, 6-, and 9-positions adopt the same configuration. Therefore, the structure of naematolin must be depicted as 1, involving 1S,2S,3R,6R, and 9S configurations.

Table 2. NOE of 2 and 5

| Compound | Irradiated | Observed | NOE/% |
|---|---|---|---|
| 2 | 12-H | 2-H | 10 |
| | 12-H | 15-Ha | 10 |
| | 13-H | 1-H | 25 |
| | 14-H | 2-H | 15 |
| | 14-H | 3-H | 15 |
| | 9-H | 6-H | 10 |
| | 9-H | 5-H | 10 |
| | 2-H | 3-H | 13 |
| | 15-Ha | 15-Hb | 32 |
| | 5-H | 6-H | 11 |
| | 5-H | 9-H | 12 |
| | 5-H | 1-H | 22 |
| 5 | 12-H | 15-Ha | 14 |
| | 12-H | 2-H | 5 |
| | 1-H | 9-H | 15 |
| | 1-H | 13-H | 21 |
| | 9-H | 1-H | 3 |
| | 9-H | 6-H | 6 |
| | 6-H | 5-H | 6 |
| | 5-H | 6-H | 7 |

This proposal has been well confirmed by an X-ray analysis of 4. A perspective drawing is given in Fig. 1, in which the ring juncture is cis, the geometry of the endocyclic double bond is trans, and the configuration is 1S,2S,3R, 6R, and 9S, respectively. This finding agrees well with the absolute configuration deduced from the above spectral data.

Crystal data were as follows: $C_{24}H_{27}O_6Br$ (MW=491.36), orthorhombic, space group $P2_12_12_1$, a=10.650(2), b=20.650(6), c=10.526(2) Å$^3$ , Z=4, Dc=1.410 Mg m$^{-3}$, μ=1.791 mm$^{-1}$. A total of 1666 reflections was recorded on a RIGAKU four-circle diffractometer with graphite-monochromatized MoKα (λ=0.71073 Å) radiation. The structure was solved by the direct method and the final R value was 0.084. The absolute configuration was determined through the anomalous dispersion effect of the bromine atom.

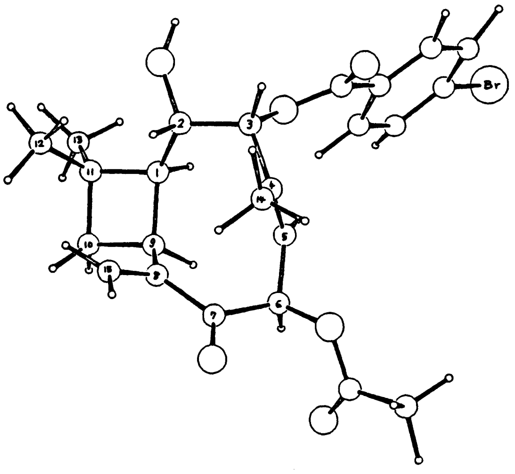
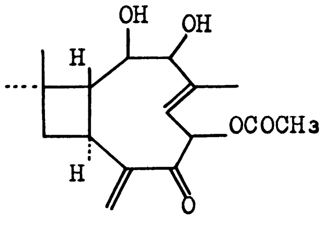


Fig. 1. A perspective drawing of 4.

The structure of naematolin B, which was deduced as 13-hydroxynaematolin from Table 1, agrees well with 5 from the NOE data cited in Table 2. An example of 12-hydroxycaryophyllane derivative has been reported as a metabolite of a mushroom.[10]

Naematolin(1) and naematolin B(5) both demonstrate the first case of 1-*epi*-caryophyllane skeleton in nature, although 9-*epi*-caryophyllane derivatives are known as plant constituents.[11]

Backens *et al.*[12] have proposed an alternate structure(6) for naematolin without any direct comparison with Ito's compound.[1] Presumably, the Backens' compound is 1-*epi*-naematolin.



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3) All molecular formulas were obtained by HRMS.
4) We wish to thank Dr.H.Kurita of Microbial Chem. Res. Lab., Tanabe Seiyaku Co.,Ltd. for his kindly gift of naematolin acetate.
5) 2D COSYs were measured on a JEOL JNM-GX 270. We thank Messr. K.Hioka, N.Fujii, and O.Kamo of NMR Application Lab., JEOL Ltd. for the measurements.
6) Y.Kashman and A.Groweiss, J.Org.Chem., 45, 3814(1980).
7) It was recorded on a JASCO J-20A spectropolarimeter in MeOH.
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