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Crystal Structue and Absolute Configuration of a New *cis*-Fused Caryophyllene Derivative. Naematlin 3-*p*-Bromobenzoate

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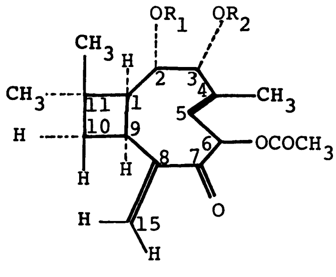
The molecular structure of naematolin 3-*p*-bromobenzoate has been determined by X-ray diffraction analysis. Unlike known caryophyllene derivatives isolated so far, the stereochemistry of the ring juncture is *cis* (1*S*,9*S*) form. The absolute configurations of five chiral centers of this compound are 1*S*,2*S*,3*R*,6*R*, and 9*S*, and the geometry of endocyclic double bond is *E* mode. This is the first example of a *cis*-fused 1*S*,9*S*-caryophyllane sesquiterpenoids confirmed by X-ray structure determination. Crystal data and the final *R* factor are: Mr=491.36, orthorhombic, space group $P2_12_12_1$, $a=10.650(2)$, $b=20.650(6)$, $c=10.526(2)$ Å, $U=2315(1)$ Å^3, $Z=4$, $D_c=1.410$ Mg m^{-3}, $\mu=1.791$ mm^{-1}, $R=0.084$ for 1666 observed unique reflections.

Naturally occurring caryophyllane sesquiterpenoids either plant or animal origins consist generally of *trans*-bicyclo[7.2.0]undecane skeleton. Some of their structures were determined by X-ray analyses.[1-8] The structure of a sesquiterpenoid naematolin isolated from *Naematoloma sublateritium* by Backens et al. was also assigned to have *trans*-fused configuration on the basis of the spectral data.[9] With only exception, 9-*epi*-caryophyllene possessing *cis*-bicyclo[7.2.0]undecane skeleton, was described by Bohlmann et al.[10]

Very recently, the structure of naematolin (**1**) has been reported to be described as **1**, indicative of 1-epimeric caryophyllene derivative.[11] This compound **1** was first isolated by Ito et al. in 1967 as one of metabolites of *Naematoloma fasciculare* (Basidiomycetes).[12]

In order to confirm the stereochemistry and to clarify the absolute configuration of naematolin, the structure determination of its 3-*p*-bromobenzoate (**2**) was carried out by X-ray analysis.



1 $R_1=R_2=H$
2 $R_1=H$, $R_2=p\text{-}BrC_6H_4CO$
3 $R_1=R_2=COCH_3$
4 $R_1=R_2=C_6H_5CO$

Experimental

Crystal Data. $C_{24}H_{27}O_6Br$, Mr=491.36, orthorhombic, space group $P2_12_12_1$, $a=10.650(2)$, $b=20.650(6)$, $c=10.526(2)$ Å, $U=2315(1)$ Å^3, $Z=4$, $D_c=1.410$ Mg m^{-3}, $\mu=1.791$ mm^{-1}.

The sample for X-ray analysis was crystallized from ether–hexane. A 0.4×0.4×0.15 mm, colorless and plate crystal, was used for the measurement. The reflections within the range of $2\theta<55°$ were collected on a Rigaku AFC-5 four-circle automated X-ray diffractometer with graphite monochromatized Mo *Kα* radiation ($\lambda=0.7073$ Å) by means of the ω scan ($2\theta<30°$) and ω—2θ scan ($2\theta>30°$) techniques. From the 2580 observed reflections, 1666 independent reflections with $|F_o|>3\sigma(F_o)$ were used for the structure analysis. The intensities were corrected for the Lorentz and polarization factors, and for the absorption. All the calculations were carried out on a FACOM M-380 computer at this Institute, using UNICS III program system.[13] The scattering factors and anomalous dispersion terms were taken from the International Tables.[14] The structure was solved by MULTAN,[15] and was refined by the block-diagonal least-squares method. The calculated hydrogen atom positions were included in the refinement with isotropic temperature factors. The final refinement was done through full-matrix least-squares method including extinction corrections with the weight $1/\sigma(F_o)^2$.[16] The final *R* was 0.084. Positional parameters for non-hydrogen atoms are given in Table 1.**

The Determination of the Absolute Configuration. The absolute configuration was determined with Mo *Kα* data. The size of the crystal was 0.5×0.5×0.28 mm.

Eleven indices with $|\Delta F_c|/\sigma(F_o)>13$ were selected for the determination of the absolute configuration, where ΔF_c is the difference between the $|F_c|$ for the Bijvoet pairs. For each index, the diffraction intensities were measured for all eight combinations of plus and minus signs, and the mean values of equivalent indices were compared with the calculations. Signs of ΔF_o agree with those of ΔF_c without exception. Thus the parameters in Table 1 represent the correct absolute configuration without doubt.

Discussion of the Structure

A perspective drawing and the bond parameters are given in Figs. 1 and 2. The structure of **2** is best described as the conformation **5** (Fig. 3), where 4-membered ring having gem dimethyl groups is fused to 9-membered ring with *cis* fashion. The 9-membered ring moiety contains hydroxyl, *p*-bromobenzoyloxyl, allylic methyl, acetoxyl, carbonyl, and exocyclic methylene groups. The geometry of endocyclic double

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** Tables of anisotropic temperature factors, atomic parameters of hydrogen atoms, and observed and calculated structure factors are kept at the Chemical Society of Japan, Document No. 8633.

Table 1. Atomic Parameters

Atom	X	Y	Z	$B_{eq}/\text{Å}^2$
BR	7020(2)	2241(1)	−1479(2)	5.7
O(2)	−253(13)	8(6)	−2564(10)	5.1
O(3)	1179(9)	927(5)	−1154(8)	3.0
O(6)	76(12)	1023(6)	3518(11)	4.6
O(7)	−1397(10)	−23(6)	3614(11)	4.6
O(16)	1071(15)	527(9)	5151(12)	6.6
O(18)	620(11)	1962(5)	−1422(14)	4.9
C(1)	529(12)	−442(6)	−614(12)	2.2
C(2)	−327(14)	66(8)	−1208(13)	3.2
C(3)	−94(15)	766(7)	−839(12)	3.0
C(4)	−364(14)	843(6)	575(15)	2.9
C(5)	608(15)	702(7)	1328(15)	3.6
C(6)	406(18)	463(8)	2709(12)	3.7
C(7)	−635(15)	−19(7)	2749(15)	3.1
C(8)	−760(14)	−500(7)	1644(16)	3.5
C(9)	378(14)	−677(6)	862(13)	2.6
C(10)	479(16)	−1375(8)	402(17)	4.2
C(11)	365(13)	−1144(8)	−1047(14)	3.2
C(12)	−893(16)	−1335(9)	−1627(19)	4.9
C(13)	1428(18)	−1413(10)	−1895(17)	5.5
C(14)	−1679(15)	955(8)	955(14)	3.9
C(15)	−1884(16)	−754(8)	1497(19)	5.2
C(16)	441(22)	977(12)	4786(19)	5.8
C(17)	−13(24)	1563(11)	5430(18)	6.9
C(18)	1430(15)	1561(7)	−1308(13)	3.2
C(19)	2793(14)	1700(6)	−1364(13)	2.8
C(20)	3171(15)	2286(8)	−1826(13)	3.5
C(21)	4418(17)	2470(7)	−1905(14)	3.9
C(22)	5294(13)	2043(7)	−1398(15)	3.4
C(23)	4945(16)	1450(8)	−860(15)	3.6
C(24)	3666(14)	1283(7)	−853(13)	2.8

Positional parameters are multiplied by 10^4. Thermal parameters are given by the equivalent temperature factors.

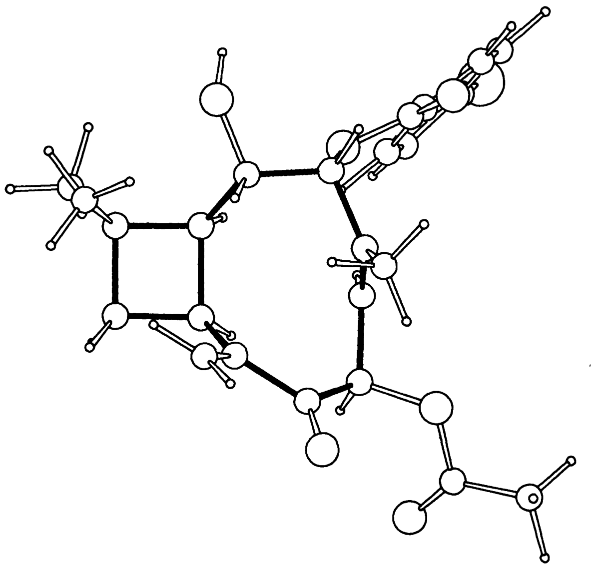
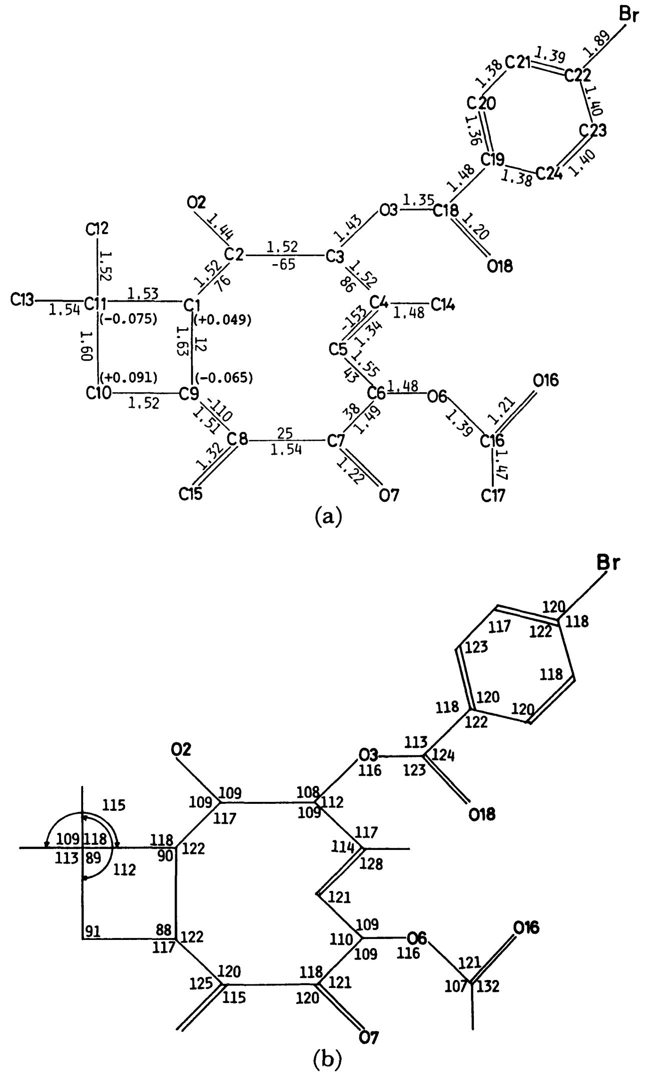


Fig. 1. Perspective drawing of the molecule.



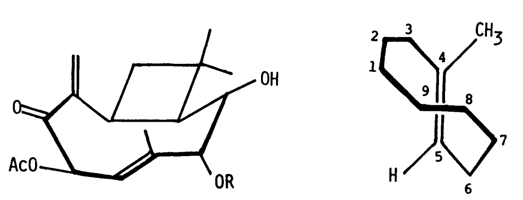
(a)

(b)

Fig. 2. Bond parameters.

(a) Bond lengths (l/Å) and torsion angles(ϕ/°). Torsion angles around the 9-membered ring are expressed by the figures inside the ring. The atomic displacements (Å) from the least-squares 4-membered plane are given in parentheses. (b) Bond angles (ϕ/°).

The standard deviations are: bond lengths: 0.03 Å; torsion angles: 2°; bond angles: 2°; atomic displacements: 0.008 Å.



5 **6**

Fig. 3. Conformation of naematolin and chirality of 9-membered ring.

bond is E mode, and the configuration of the sp^2 plane chirality arising from the double bond is R as illustrated in **6**. (Fig. 3). Thus the configurations of the present compound are 1S, 2S, 3R, 4E, 6R, and 9S, respectively. Although *cis*-1R,9R-fused related compound has already been known as described above,[10] this is the first example of a *cis*-fused 1S,9S-caryophyllane sesquiterpenoid. The result agrees well with the stereochemistry deduced from the spectral data, and the application of the dibenzoate chirality rule[17] to the dibenzoate **4** led also to the same conclusion.[11]

The markedly short nonbonded contacts are found between C(4) and C(8), and C(5) and C(8), 3.02(2), 2.90(2) Å, respectively. In fact, transannular cyclization in caryophyllene system occurs to give β-caryophyllene alcohol or the other tricyclic derivatives.[1,2,5]

Very large transannular H–H repulsions are supposed among hydrogen atoms H(C9), H(C5), and H(C6), and H(C2), H(C15-2) and H(C12-1) as observed by NOE experiments of ^{1}H NMR of the diacetate **3**.[11] The transannular hydrogen interactions may relieve even slightly by deviation of bond angle from the normal tetrahedral one and the carbonyl group occupies corner position. The conformation of fused 4-membered ring is essentially planar as given in Fig. 2(a), although that of *trans*-fused caryophyllene is usually nonplanar. The bond angles keep nearly 90°, and the fairly long bond lengths are observed between C(1) and C(9), and C(10) and C(11). This elongation of the bond lengths may release the repulsion between them.

The 9-membered ring takes [13113]*** and a boat-chair (BC) conformation as shown in Fig. 4. The lowest calculated conformation for flexible unsubstituted and saturated cyclononane is the triangular [333] and twist boat-chair (TBC) form of D_3 symmetry.[18] The corresponding cyclic ketone, cyclononanone, in a crystalline $HgCl_2$ complex has been shown to take an unsymmetric, quinquangular of type [12222], and a twist chair-boat (TCB) conformation of C_2 symmetry.[19,20] However, the ring in the present compound forces to take the BC conformation by the steric requirement.

β,γ-Unsaturated carbonyl compound can form inherently chiral chromophoric system.[21] In the circular dichroism spectrum of **1**, the negative relatively high rotational strength, $\Delta\varepsilon_{327}$ −3.16°, originates probably from this chirality. The sign of the n-π^* Cotton effect agrees with the negative direction in the chirality rule as shown in Fig. 5. The dihedral angle of two planes in **2** is found to be 112°.

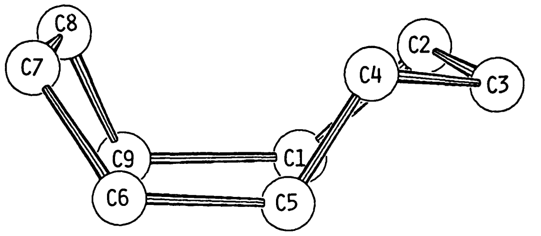


Fig. 4. Conformation of 9-membered ring.

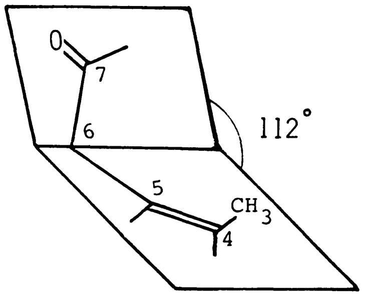


Fig. 5. Helicity with respect to β,γ-unsaturated ketone.

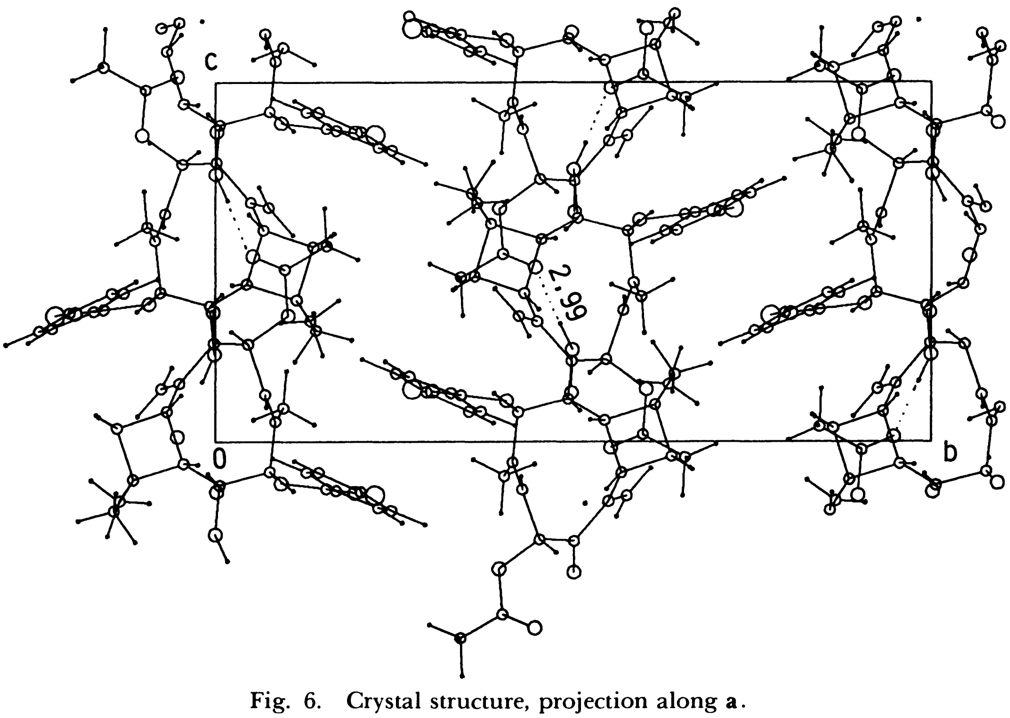


Fig. 6. Crystal structure, projection along **a**.

*** The conformation type is expressed by a series of numbers within brackets, each giving the number of bonds in one side. (Y. Dale, *Acta Chem. Scand.*, **27**, 115 (1973)).

Conjugation of an α,β-unsaturated ketone tends to keep coplanarity unless a steric repulsion exists. In **2**, however, the terminal double bond and keto group are twisted to each other (23°). This means that a planar geometry is prevented by the unusual highly strained ring conformation. The deformation from coplanarity causes decrease in the optical density at the maximum in absorption spectrum of **1** compared with that of an isomer of naematolin, which was assgined to have trans juncture.[9]

Only one relatively weak intermolecular hydrogen bond is observed between O(2) and O(16), 2.99(2) Å, and there is no short (<3.3 Å) intermolecular contacts as shown in Fig. 6. The relatively large R index may be due to the low-density packing.

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References

1) K. M. Robertson, and G. Todd, *J. Chem. Soc.*, **1955**, 1254.

2) D. M. Hawley, G. Ferguson, *J. Chem. Soc., (B)*, **1968**, 1255.

3) R. B. Bates, G. D. Rorsythe, G. A. Wolfe, G. Ohloff, and K.-H. Schulte-Eyte, *J. Org. Chem.*, **34**, 1059 (1969).

4) K. W. Gemmell, W. Parker, J. S. Roberts, and J. M. Robertson, *J. Chem. Soc., (B)*, **1970**, 947.

5) M-ul-Haque, D. Rogers, *J. Chem. Soc., Perkin Trans. 2*, **1974**, 228.

6) T. Yoshida, J. Nobuhara, M. Uchida, and T. Okuda, *Chem. Pharm. Bull.*, **26**, 2535 (1978).

7) Y. Asakawa, Z. Taira, T. Takemoto, T. Ishida, M. Kido, and Y. Ichikawa, *J. Pharm. Sci.*, **70**, 710 (1981).

8) W. M. Daniewski, P. A. Grieco, J. C. Huffman, A. Rymkiewcz, and A. Wawrzun, *Phytochem.*, **20**, 2733 (1981).

9) S. Backens, B. Steffan, W. Steglich, L. Zechlin, and T. Anke, *Liebigs Ann. Chem.*, **1984**, 1332.

10) F. Bohlmann, and C. Zdero, *Phytochem.*, **17**, 1135 (1978).

11) K. Doi, T. Shibata, M. Nara, S. Tsuboyama, T. Sakurai, and K. Tsuboyama, *Chem. Lett.*, **1986**, 653.

12) Y. Ito, H. Kurita, T. Yamaguchi, M, Sato, and T. Okuda, *Chem. Pharm. Bull.*, **15**, 2009 (1967).

13) T. Sakurai, and K. Kobayashi, *Rikagaku Kenkyusho Hokoku*, **55**, 69 (1979).

14) "International Tables for X-Ray Crystallography," Vol. IV. Birmingham (1974): Kynoch Press.

15) P. Main, S. E. Hull, L. Lessinger, G. Germain, J.-P. Declercq, and M. M. Woolfson (1978). *MULTAN* **78**. A "System of Computer Programs for the Automatic Solution of Crystal Structures from X-Ray Diffraction Data," Univs. of York, England, and Louvain, Belgium.

16) P. J. Backer, and P. Coppens, *Acta Crystallogr., Sect. A*, **31**, 417 (1975).

17) N. Harada, and K. Nakanishi, *Acc. Chem. Res.* **5**, 257 (1972).

18) F. A. L. Anet, and J. J. Wagner, *J. Am. Chem. Soc.*, **93**, 5266 (1971).

19) S. Dahl, and P. Groth, *Acta Chem. Scand.*, **25**, 1114 (1971).

20) Y. Dale, *Top. Stereochem.*, **9**, 199 (1976).

21) A. Moscowitz, K. Mislow, M. A. W. Glass, C. Djerassi, *J. Am. Chem. Soc.*, **84**, 1945 (1962).