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The sesquiterpenoid nootkatone and the absolute configuration of a dibromo derivative

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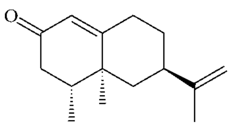
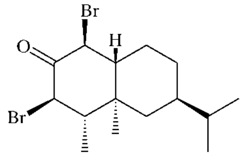
Nootkatone, or (4*R*,4a*S*,6*R*)-4,4a,5,6,7,8-hexahydro-4,4a-dimethyl-6-(1-methylethenyl)naphthalen-2(3*H*)-one, $C_{15}H_{22}O$, a sesquiterpene with strong repellent properties against Formosan subterranean termites and other insects, has the valencene skeleton. The dibromo derivative (1*S*,3*R*,4*S*,4a*S*,6*R*,8a*R*)-1,3-dibromo-6-isopropyl-4,4a-dimethyl-1,2,3,4,5,6,7,8-octahydronaphthalen-2-one, $C_{15}H_{24}Br_2O$, has two independent molecules in the asymmetric unit, which differ in the rotation of the isopropyl group with respect to the main skeleton. The C—Br distances are in the range 1.950 (4)–1.960 (4) Å. Both independent molecules form zigzag chains, with very short intermolecular carbonyl–carbonyl interactions, having the perpendicular motif and O···C distances of 2.886 (6) and 2.898 (6) Å. These chains are flanked by intermolecular Br···Br interactions of distances in the range 4.067 (1)–4.218 (1) Å. The absolute configuration of the dibromo derivative was determined, from which that of nootkatone was inferred.

Comment

Nootkatone, (I), the major flavorant of grapefruit, is a valencene-class sesquiterpene ketone, which was first isolated from Alaskan yellow cedar (Erdtman & Hirose, 1962) and is a minor component of some vetiver oils. Part of the interest in this class of compounds is due to their termiticidic and insect repellent activity, particularly towards the Formosan subterranean termite (Zhu, Henderson, Chen, Fei & Laine, 2001; Zhu, Henderson, Chen, Fei, Maistrello & Laine, 2001). Nootkatone appears to be non-toxic to humans, and it is currently added to juices to impart a grapefruit essence. We have been studying nootkatone because of its potent and seemingly receptor-specific activity, and also because of its potential commercial importance as a termiticide. Since absolute structure is usually an important factor controlling biological activity, we have determined the crystal structure of this low-melting (m.p. 309–311 K) natural product and sought to definitively establish its absolute structure. We are not aware of any previous absolute structure determinations by X-ray methods of valencene-class sesquiterpenoids or those of the eremophilene class, which differ from the valencenes by the configuration at C4 and C5. To this end, we attempted to synthesize a bromo derivative of nootkatone, but were unsuccessful in growing suitable crystals of any such compounds. We thus turned to bromination of tetrahydronootkatone, which has the same absolute configuration, because a published synthesis of 3-α-bromotetrahydronootkatone (m.p. 353–351 K) was available (MacLeod, 1965). In our hands, the MacLeod synthesis did not yield the expected product, but instead yielded compound (II) (m.p. 406–408 K; Sauer *et al.*, 2003), a dibromo derivative. Fortunately, this compound crystallized well and was sufficient for absolute configuration determination. We report here the low-temperature structures of both nootkatone, (I) (150 K), and the dibromo derivative (II) (100 K).



(I)



(II)

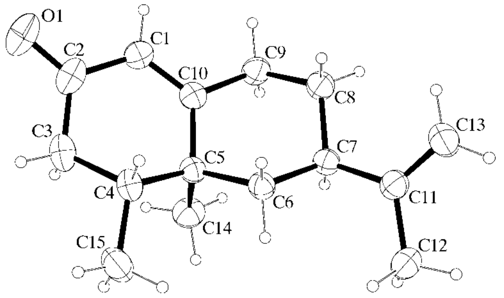


Figure 1
View of the molecule of nootkatone, (I), showing the atom-numbering scheme and ellipsoids at the 50% probability level.

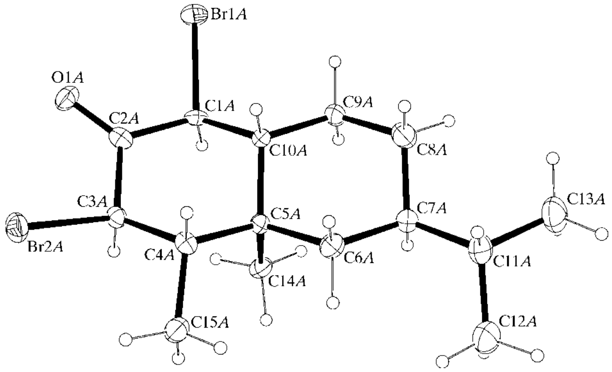


Figure 2
View of one of the two independent molecules of (II), showing the atom-numbering scheme and ellipsoids at the 50% probability level.

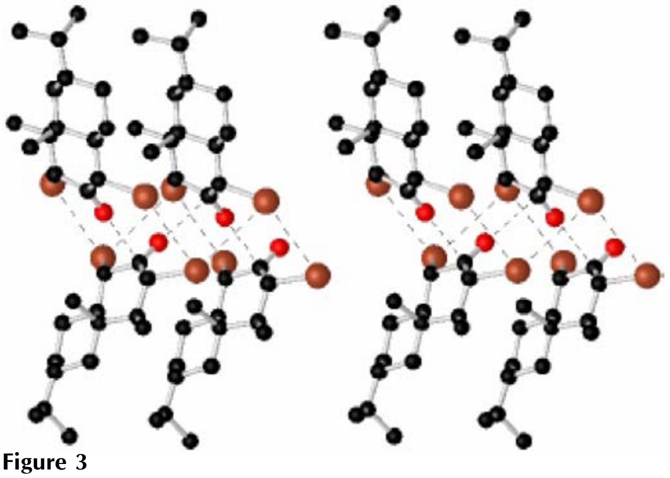


Figure 3
Stereopair of intermolecular interactions for the *B* molecule of (II). Carbonyl–carbonyl and Br···Br interactions are dashed and H atoms are not shown.

The structure of (I) is shown in Fig. 1, which illustrates its valencene-type skeleton, with methyl groups C14 and C15 α-oriented, and the substituent at C7 β-oriented. The C5–C10 ring is in a slightly flattened chair conformation, with endocyclic torsion angles in the range 45.3 (2)–57.5 (2)°, the flattening being a result of the C1═C10 double bond (Table 1). The presence of the C1═C10 unsaturation in the other ring and the ketone group conjugated to it causes it to have a conformation in which all atoms except C4 are nearly coplanar. Atom C4 lies 0.624 (2) Å out of the best plane of the other five atoms, which exhibit a maximum deviation of 0.074 (2) Å for C2. The packing for (I) is unremarkable; in particular, the molecules do not form carbonyl–carbonyl intermolecular interactions of the type described by Allen *et al.* (1998). The absolute configuration of (I) is inferred to be that shown in Fig. 1, corresponding to the configuration directly determined for (II). The skeleton of nootkatone is shared with tetrahydronootkatone, vetivone and valencene, all of which have the same configuration. All have strong repellent properties against the Formosan subterranean termite except for valencene, which lacks the C2-ketone group and is relatively inactive. Thus, we conclude that the binding site must recognize the stereochemistry of the skeleton, but require the ketone.

The absolute structure of (II) is shown in Fig. 2, which illustrates one of the two independent molecules. There are no significant differences between corresponding bond distances in the two molecules or between their endocyclic torsion angles (Table 2). Both rings in the molecule have chair conformations; that carrying the ketone is slightly flattened, with endocyclic torsion angles in the range 40.5 (5)–64.5 (5)°, while the other ring is much less flattened compared with that of (I), having torsion angles in the range 52.6 (5)–60.0 (5)°. The main difference between molecules *A* and *B* is in the rotation of the isopropyl group with respect to the main skeleton. The difference in rotation is 125.2 (8)°, such that C13 is *anti* to C6 in molecule *A* and *anti* to C8 in molecule *B*.

The most remarkable feature of the structure of (II) is its packing. Both independent molecules form zigzag chains of carbonyl–carbonyl intermolecular interactions in the [010] direction, propagated by 2_1 axes. The geometry of the interactions is the perpendicular motif, which is reported by Allen *et al.* (1998) to occur in about 1.3% of the carbonyl-containing structures in the Cambridge Structural Database (Allen, 2002). The C═O···C angles here are nearly linear, with $C2A{=}O1A\cdots C2A^{i}$ = 176.4 (4)° and $C2B{=}O1B\cdots C2B^{ii}$ = 175.8 (4)° [symmetry codes: (i) $1-x, \frac{1}{2}+y, 1-z$; (ii) $-x, \frac{1}{2}+y, -z$]. The C···O distances are much shorter than expected [2.886 (6) Å for the the *A* chain and 2.898 (6) Å for the *B* chain], representing some of the shortest such interactions known. Allen *et al.* (1998) reported that only 26% of such interactions are shorter than the sum of van der Waals radii for C and O (3.22 Å), with a median of 3.35 Å. The shortness of these contacts may be related to the fact that the ketone substituent is flanked by two C—Br bonds, both of which are equatorial on the six-membered ring. Thus, each carbonyl–carbonyl interaction is accompanied by two intermolecular Br···Br interactions. These distances are 4.067 (1) and 4.218 (1) Å for the *A* chain, and 4.147 (1) and 4.172 (1) Å for the *B* chain (Fig. 3), slightly longer than 3.70 Å, which is twice the van der Waals radius of Br (Bondi, 1964).

Experimental

A sample of (+)-nootkatone, $[\alpha]_D$ = +166°, was purchased from Aromor Inc., Israel. A suitable single crystal was chosen and was not recrystallized. To a solution of tetrahydronootkatone (0.5 g, 2.25 mmol), also obtained from Aromor Inc., in glacial acetic acid (11 ml) was added 1 equivalent of a 1 *M* solution of Br_2 in acetic acid. The solution was stirred at room temperature for 1 h under a positive N_2 pressure. The reaction mixture was then poured over water and extracted with $CHCl_3$. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated to give a thick oil. The dibromo derivative [(II), m.p. 406–408 K, $[\alpha]_D$ = +0.28°] was crystallized from hexanes (0.531 g, 32.6% yield).

Compound (I)

Crystal data

$C_{15}H_{22}O$
M_r = 218.33
Monoclinic, $P2_1$
a = 5.903 (2) Å
b = 9.495 (4) Å
c = 11.630 (6) Å
β = 96.09 (2)°
V = 648.2 (5) Å^3
Z = 2

D_x = 1.119 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 1493 reflections
θ = 2.5–27.5°
μ = 0.07 mm^{-1}
T = 150 K
Needle fragment, colorless
0.32 × 0.25 × 0.20 mm

Table 1
Selected geometric parameters (Å, °) for (I).

O1—C2	1.228 (3)	C11—C13	1.323 (3)
C1—C10	1.341 (3)	C11—C12	1.501 (3)
C1—C2	1.457 (4)		
C10—C1—C2—C3	−8.1 (3)	C7—C8—C9—C10	55.0 (3)
C1—C2—C3—C4	37.9 (3)	C2—C1—C10—C5	−2.9 (3)
C2—C3—C4—C5	−57.5 (3)	C8—C9—C10—C5	−49.8 (3)
C3—C4—C5—C10	45.9 (2)	C4—C5—C10—C1	−16.7 (3)
C10—C5—C6—C7	−49.6 (2)	C6—C5—C10—C9	45.3 (2)
C5—C6—C7—C8	57.2 (2)	C6—C7—C11—C12	63.4 (2)
C6—C7—C8—C9	−57.5 (2)		

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Data collection

Nonius KappaCCD diffractometer (with an Oxford Cryosystems Cryostream cooler)
ω scans with κ offsets
7526 measured reflections
1577 independent reflections

1202 reflections with $I > 2\sigma(I)$
$R_{\rm int} = 0.023$
$\theta_{\max} = 27.5°$
$h = -7 \rightarrow 7$
$k = -12 \rightarrow 12$
$l = -15 \rightarrow 15$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.041$
$wR(F^2) = 0.098$
$S = 1.06$
1577 reflections
149 parameters
H-atom parameters constrained

$w = 1/[\sigma^2(F_o^2) + (0.0459P)^2 + 0.0440P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\max} < 0.001$
$\Delta\rho_{\max} = 0.16$ e Å^{-3}
$\Delta\rho_{\min} = -0.15$ e Å^{-3}
Extinction correction: *SHELXL*97
Extinction coefficient: 0.041 (9)

Compound (II)

Crystal data

$C_{15}H_{24}Br_2O$
$M_r = 380.16$
Monoclinic, $P2_1$
$a = 13.500$ (3) Å
$b = 6.1403$ (10) Å
$c = 18.909$ (5) Å
$\beta = 92.145$ (7)°
$V = 1566.3$ (6) Å^3
$Z = 4$

$D_x = 1.612$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 4844 reflections
$\theta = 2.5$–$30.5°$
$\mu = 5.16$ mm^{-1}
$T = 100$ K
Needle, colorless
0.30 × 0.05 × 0.02 mm

Data collection

Nonius KappaCCD diffractometer (with an Oxford Cryosystems Cryostream cooler)
ω scans with κ offsets
Absorption correction: multi-scan (*HKL SCALEPACK*; Otwinowski & Minor, 1997)
$T_{\min} = 0.385$, $T_{\max} = 0.902$

19 375 measured reflections
9388 independent reflections
7482 reflections with $I > 2\sigma(I)$
$R_{\rm int} = 0.063$
$\theta_{\max} = 30.5°$
$h = -19 \rightarrow 19$
$k = -8 \rightarrow 8$
$l = -27 \rightarrow 26$

Table 2
Selected geometric parameters (Å, °) for (II).

Br1*A*—C1*A*	1.959 (4)	Br1*B*—C1*B*	1.960 (4)
Br2*A*—C3*A*	1.956 (4)	Br2*B*—C3*B*	1.950 (4)
O1*A*—C2*A*	1.207 (6)	O1*B*—C2*B*	1.203 (6)
C10*A*—C1*A*—C2*A*—C3*A*	−44.8 (5)	C10*B*—C1*B*—C2*B*—C3*B*	−44.4 (5)
C1*A*—C2*A*—C3*A*—C4*A*	41.1 (6)	C1*B*—C2*B*—C3*B*—C4*B*	40.5 (5)
C2*A*—C3*A*—C4*A*—C5*A*	−48.1 (5)	C2*B*—C3*B*—C4*B*—C5*B*	−48.4 (5)
C3*A*—C4*A*—C5*A*—C10*A*	58.1 (5)	C3*B*—C4*B*—C5*B*—C10*B*	59.1 (5)
C10*A*—C5*A*—C6*A*—C7*A*	−55.3 (5)	C10*B*—C5*B*—C6*B*—C7*B*	−56.0 (5)
C5*A*—C6*A*—C7*A*—C8*A*	56.6 (5)	C5*B*—C6*B*—C7*B*—C8*B*	60.0 (5)
C6*A*—C7*A*—C8*A*—C9*A*	−55.7 (5)	C6*B*—C7*B*—C8*B*—C9*B*	−59.1 (5)
C7*A*—C8*A*—C9*A*—C10*A*	57.4 (5)	C7*B*—C8*B*—C9*B*—C10*B*	58.9 (6)
C2*A*—C1*A*—C10*A*—C5*A*	56.7 (5)	C2*B*—C1*B*—C10*B*—C5*B*	57.0 (5)
C8*A*—C9*A*—C10*A*—C5*A*	−55.7 (5)	C8*B*—C9*B*—C10*B*—C5*B*	−55.5 (5)
C4*A*—C5*A*—C10*A*—C1*A*	−63.5 (5)	C4*B*—C5*B*—C10*B*—C1*B*	−64.5 (5)
C6*A*—C5*A*—C10*A*—C9*A*	52.9 (5)	C6*B*—C5*B*—C10*B*—C9*B*	52.6 (5)
C6*A*—C7*A*—C11*A*—C12*A*	65.9 (6)	C6*B*—C7*B*—C11*B*—C12*B*	−59.3 (6)

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.053$
$wR(F^2) = 0.095$
$S = 1.10$
9388 reflections
333 parameters
H-atom parameters constrained

$w = 1/[\sigma^2(F_o^2) + 4.9110P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\max} = 0.001$
$\Delta\rho_{\max} = 1.09$ e Å^{-3}
$\Delta\rho_{\min} = -0.66$ e Å^{-3}
Absolute structure: Flack (1983), 4216 Friedel pairs
Flack parameter = 0.019 (11)

H atoms were treated as riding in idealized positions, with C—H distances in the range 0.95–1.00 Å, depending on the atom type. A torsional parameter was refined for each methyl group. Displacement parameters for H atoms were assigned as $U_{\rm iso} = 1.2U_{\rm eq}$ of the attached atom (1.5 for methyl groups). Friedel pairs were averaged for (I). All residual peaks greater than 0.69 e Å^{-3} were within 1.1 Å of Br-atom positions.

For both compounds, data collection: *COLLECT* (Nonius, 2000); cell refinement: *DENZO* and *SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO* and *SCALEPACK*; program(s) used to solve structure: *SIR*97 (Altomare *et al.*, 1999); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*-3 (Farrugia, 1997) and *CrystMol* (Duchamp, 1999); software used to prepare material for publication: *SHELXL*97.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SQ1013). Services for accessing these data are described at the back of the journal.

References

Allen, F. H. (2002). *Acta Cryst.* B**58**, 380–388.
Allen, F. H., Baalham, C. A., Lommerse, J. P. M. & Raithby, P. R. (1998). *Acta Cryst.* B**54**, 320–881.
Altomare, A., Burla, M. C., Camalli, M., Cascarano, G., Giacovazzo, C., Guagliardi, A., Moliterni, A. G. G., Polidori, G. & Spagna, R. (1999). *J. Appl. Cryst.* **32**, 115–119.
Bondi, A. (1964). *J. Phys. Chem.* **68**, 441–451.
Duchamp, D. J. (1999). *CrystMol*. Version 1.0β. Kalamazoo, Michigan, USA.
Erdtman, H. & Hirose, Y. (1962). *Acta Chem. Scand.* **16**, 1311–1314.
Farrugia, L. J. (1997). *J. Appl. Cryst.* **30**, 565.
Flack, H. D. (1983). *Acta Cryst.* A**39**, 876–881.
MacLeod, W. D. (1965). *Tetrahedron Lett.* **52**, 4779–4783.
Nonius (2000). *COLLECT*. Nonius BV, Delft, The Netherlands.
Otwinowski, Z. & Minor, W. (1997). *Methods in Enzymology*, Vol. 276, *Macromolecular Crystallography*, Part A, edited by C. W. Carter Jr & R. M. Sweet, pp. 307–326. New York: Academic Press.
Sauer, A. M., Crowe, W. E., Laine, R. A. & Henderson, G. (2003). *J. Org. Chem.* In preparation.
Sheldrick, G. M. (1997). *SHELXL*97. University of Göttingen, Germany.
Zhu, B. C. R., Henderson, G., Chen, F., Fei, H. & Laine, R. A. (2001). *J. Chem. Ecol.* **27**, 1617–1625.
Zhu, B. C. R., Henderson, G., Chen, F., Fei, H., Maistrello, L. & Laine, R. A. (2001). *J. Chem. Ecol.* **27**, 523–531.

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