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The Crystal and Molecular Structure of 3-(1,4-Epoxy-2-hydroxy-2,6,6-trimethylcyclohexyl)-1-methyl-2-propyl *p*-Nitrobenzoate

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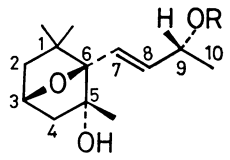
The relative configuration of natural 3,6-epoxy-5-hydroxy-5,6-dihydro-β-ionol, $C_{13}H_{22}O_3$, a principal tobacco constituent, has been established by an X-ray crystal structure analysis of its *p*-nitrobenzoate, $C_{20}H_{25}NO_6$, as (±)-(1*R*,2*R*,5*S*)-2,5-epoxy-2-[(1*E*,3*S*)-3-hydroxy-1-butenyl]-1,3,3-trimethyl-1-cyclohexanol. The derivative crystallizes in space group $P\bar{1}$ with $a=11.618(1)$, $b=12.373(2)$, $c=7.934(1)$ Å, $\alpha=108.43(1)$, $\beta=108.89(1)$, $\gamma=95.95(1)°$ and $Z=2$. The crystal structure was solved by the direct phasing method and refined by the block-diagonal least-squares method to the final *R* index of 0.073 for 2550 reflections. The hydrogen bondings linking the two molecules placed in pairs around a crystallographic center of symmetry are disordered over two sites in the crystal.

A novel flavor substance, (−)-3,6-epoxy-5-hydroxy-5,6-dihydro-β-ionol (**1**), was initially found in the volatile fraction of air-cured Japanese Suifu tobacco.[1] Enzell *et al.* also isolated the compound **1** from sun-cured Greek tobacco and established the relative configurations at C-3, C-5, and C-6, but the configuration at the remaining asymmetric center, C-9, remained unsettled.[2] In order to establish this relative configuration at C-9, the crystalline *p*-nitrobenzoate derivative **2** was synthesized and subjected to a single crystal X-ray diffraction analysis. A brief account on this work has appeared previously.[3]



1 R=H

2 R=*p*-Nitrobenzoyl

Experimental

The title compound was crystallized from a hexane solution as colorless plates elongated along the b direction. A well-shaped crystal of dimensions $0.05\times0.3\times0.2$ mm³ was mounted with the b axis coincident with the goniometer ϕ axis and used for the X-ray measurements. Preliminary unit cell dimensions and space group information were obtained from oscillation and Weissenberg photographs. Accurate cell dimensions were obtained by a least-squares fit of the 2θ values of 25 reflections measured on a Rigaku automated four-circle diffractometer. Intensity data were also collected on this instrument using graphite-monochromated Cu $K\alpha$ radiation and 2θ-ω scanning mode at a rate of $10°(\omega)$/min with a scan range of $(0.8+0.142\tan\theta)°(\omega)$. As a check on the crystal and electronic stability, three representative reflections were measured after every 50 measurements. The intensities of these standards decreased gradually during the data collection. A total of 2550 unique reflection intensities were collected up to $2\theta=120°$ with the criterion $F\geqq3\sigma(F)$; these were corrected for crystal deterioration and for Lorentz and polarization effects, but not for absorption.

Crystal Data. $C_{20}H_{25}NO_6$, M.W.=375.41, triclinic, space group $P\bar{1}$, $a=11.618(1)$, $b=12.373(2)$, $c=7.934(1)$ Å, $\alpha=108.43(1)$, $\beta=108.89(1)$, $\gamma=95.95(1)°$, $V=996.51$ Å³, $D_m=1.24$, and $D_x=1.252$ Mg m^{-3} for $Z=2$, μ(Cu $K\alpha$)=7.76 cm^{-1}.

Structure Determination and Refinement

The structure was solved by the multiple-solution tangent formula program MULTAN 78.[4] The phase set with the highest combined figure of merit gave a reasonable structure containing all the atoms except one. Successive Fourier and difference Fourier maps revealed all the remaining atoms including hydrogen atoms. The parameters were refined by the block-diagonal least-squares program HBLS V.[5] The final refinement in which anisotropic temperature factors were assumed for the non-hydrogen atoms and isotropic ones for the hydrogen atoms gave $R=0.073$ for 2550 reflections. In the refinement the function minimized was $\Sigma\omega(|F_o|-|F_c|)^2$ with $\omega=(\sigma^2(F_o)+a|F_o|+b|F_o|^2)^{-1}$ where $\sigma(F_o)$ is the standard deviation based on counting statistics. The final values of *a* and *b* were −0.1262 and 0.0029 respectively. The atomic scattering factors were taken from International Tables for X-Ray Crystallography.[6] Final positional and thermal parameters of the atoms are listed in Tables 1 and 2.[7]

Discussion

A stereodrawing of the molecule is shown in Fig. 1. Figure 2 shows the atomic labelling and the bond lengths and angles for non-hydrogen atoms. Bond lengths and angles involving hydrogen atoms are shown in Table 3. The conformations around the C(6)–C(1) and C(6)–C(5) bonds are shown in Fig. 3 as the Newmann projections. Further details of the molecular geometry are given in Table 4. The estimated standard deviations of the bond lengths for non-hydrogen atoms are 0.006—0.009 Å, while those of the bond angles are 0.4—0.6°.

Since the atoms C(3) and C(6) are bridged by an epoxyl O(1) atom, the cyclohexane ring adopts a boat conformation. The epoxyl bridge plane C(3)–O(1)–C(6) bisects the cyclohexane ring at the dihedral angles of 124.8° and 118.2° to the C(6)–C(1)–C(2)–C(3) plane and C(3)–C(4)–C(5)–C(6) planes respectively. The O(2)H and C(12)H_3 groups are axially attached to the cyclohexane ring; this severe 1,3-

TABLE 1. POSITIONAL($\times 10^4$) AND THERMAL ($\times 10$) PARAMETERS FOR THE NON-HYDROGEN ATOMS

Atom	x	y	z	B_{eq}/Å^2 a)
C(1)	5139(4)	2822(4)	7067(7)	53
C(2)	5121(5)	1533(4)	5946(8)	68
C(3)	6240(6)	1692(4)	5406(8)	69
C(4)	5935(6)	2151(4)	3717(8)	73
C(5)	6062(4)	3450(4)	4789(7)	51
C(6)	6277(4)	3496(3)	6896(6)	45
C(7)	6856(4)	4680(4)	8395(6)	45
C(8)	8034(4)	5070(4)	9625(6)	48
C(9)	8521(4)	6282(4)	11063(6)	51
C(10)	9272(6)	6347(6)	13054(8)	82
C(11)	5495(6)	2997(4)	9220(7)	67
C(12)	3873(5)	3160(4)	6329(8)	65
C(13)	7185(5)	4206(5)	4799(8)	68
C(14)	8888(4)	7529(4)	9454(8)	64
C(15)	9823(5)	8178(4)	9001(7)	58
C(16)	11094(4)	8268(4)	9887(7)	60
C(17)	11943(5)	8935(4)	9532(8)	65
C(18)	11507(5)	9506(4)	8278(8)	63
C(19)	10239(5)	9421(4)	7358(7)	62
C(20)	9404(5)	8760(4)	7743(7)	62
N	12411(4)	10223(4)	7910(7)	76
O(1)	7115(3)	2723(2)	6999(4)	55
O(2)	4990(3)	3850(3)	3933(5)	60
O(3)	9379(3)	6939(3)	10560(5)	59
O(4)	7782(3)	7530(3)	8833(6)	78
O(5)	13523(4)	10358(3)	8820(7)	86
O(6)	12013(5)	10641(4)	6667(7)	106

a) The equivalent isotropic temperature factor defined by W. C. Hamilton (*Acta Crystallogr.*, **12**, 609 (1959)).

TABLE 2. POSITIONAL($\times 10^3$) AND ISOTROPIC THERMAL ($\times 10$) PARAMETERS FOR THE HYDROGEN ATOMS

Atom	x	y	z	B/Å^2
H1(C2)	512(5)	104(5)	689(8)	67(15)
H2(C2)	416(5)	102(4)	483(7)	64(14)
H(C3)	675(4)	107(4)	525(6)	39(11)
H1(C4)	656(4)	211(3)	332(5)	26(9)
H2(C4)	503(5)	158(5)	254(8)	66(14)
H(C7)	638(4)	530(3)	830(6)	28(9)
H(C8)	859(4)	436(3)	966(6)	32(10)
H(C9)	792(3)	678(3)	1110(5)	22(9)
H1(C10)	975(4)	585(3)	1301(6)	31(10)
H2(C10)	865(4)	572(4)	1339(6)	40(11)
H3(C10)	963(5)	732(5)	1387(7)	65(14)
H1(C11)	554(4)	382(4)	996(7)	48(12)
H2(C11)	493(5)	235(4)	930(7)	57(13)
H3(C11)	637(5)	278(5)	957(7)	66(15)
H1(C12)	395(4)	395(3)	691(6)	27(9)
H2(C12)	333(4)	276(4)	655(7)	52(13)
H3(C12)	371(5)	279(4)	475(7)	61(14)
H1(C13)	789(4)	414(4)	538(6)	36(10)
H2(C13)	715(5)	511(5)	551(7)	65(14)
H3(C13)	723(4)	413(4)	361(6)	36(10)
H(C16)	1124(5)	768(4)	1077(7)	60(14)
H(C17)	1291(4)	897(4)	1004(7)	53(13)
H(C19)	979(6)	1007(6)	653(9)	92(18)
H(C20)	852(5)	893(4)	756(7)	65(14)
H1(O2)a)	507(10)	468(7)	466(14)	35(22)
H2(O2)a)	434(10)	292(10)	319(15)	71(31)

a) Occupancy factor 0.5.

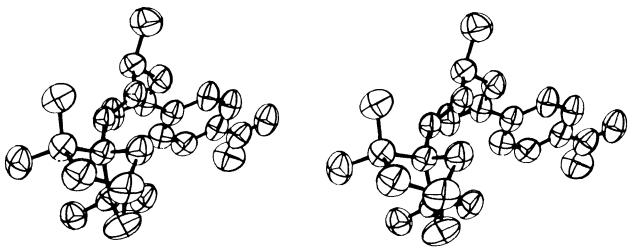


Fig. 1. A stereodrawing of the molecule viewed along the b axis.
The thermal ellipsoids correspond to 50% probability.

diaxial interaction results in an enlargement of the C(6)–C(5)–O(2), C(1)–C(6)–C(5), and C(6)–C(1)–C(12) bond angles (114.5, 114.4, and 116.8° respectively). In the side chain, the atoms C(6), C(7), C(8), and C(9) make a plane, the C(8) and O(1) atoms being synperiplanar about the C(6)–C(7) bond, while the atoms C(10) and O(3) deviate significantly from this plane onto the opposite sides; the torsion angles C(7)–C(8)–C(9)–C(10) and C(7)–C(8)–C(9)–O(3) are 132.9° and −110.0° respectively. The mean C–C length of 1.549 Å in the cyclohexane ring agrees well with the expected value and the three methyl carbons also have a reasonable mean bond length of 1.543 Å. The epoxyl O(1)–C(3) and O(1)–C(6)

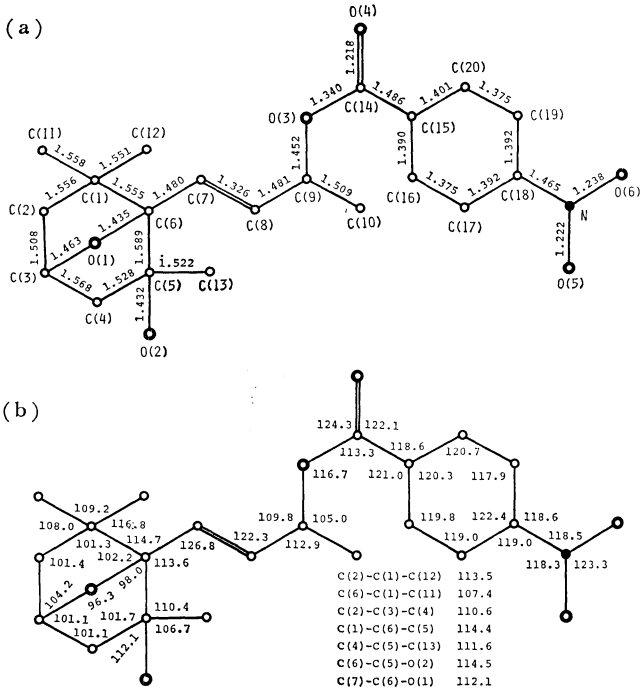
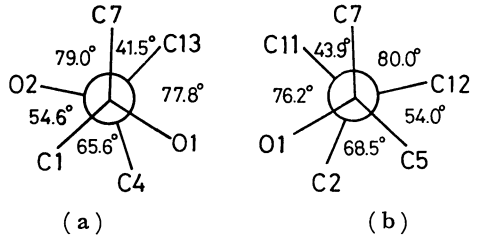


Fig. 2. A schematic drawing of the molecule showing (a) the bond lengths (l/Å) and (b) the bond angles (ϕ/°), together with atomic numbering.

TABLE 3. BOND LENGTHS AND ANGLES INVOLVING THE HYDROGEN ATOMS

Bond length	l/Å		l/Å
C(2)-H1(C2)	1.11(6)	C(2)-H2(C2)	1.13(6)
C(3)-H(C3)	1.02(5)	C(4)-H1(C4)	0.89(4)
C(4)-H2(C4)	1.13(6)	C(7)-H(C7)	1.00(4)
C(8)-H(C8)	1.15(5)	C(9)-H(C9)	0.98(4)
C(10)-H1(C10)	0.87(5)	C(10)-H2(C10)	1.15(5)
C(10)-H3(C10)	1.13(6)	C(11)-H1(C11)	0.99(5)
C(11)-H2(C11)	1.02(6)	C(11)-H3(C11)	1.05(6)
C(12)-H1(C12)	0.92(5)	C(12)-H2(C12)	0.85(5)
C(12)-H3(C12)	1.13(6)	C(13)-H1(C13)	0.83(5)
C(13)-H2(C13)	1.09(6)	C(13)-H3(C13)	0.94(5)
C(16)-H(C16)	1.15(6)	C(17)-H(C17)	1.06(5)
C(19)-H(C19)	1.24(7)	C(20)-H(C20)	1.05(6)
O(2)-H1(O2)	0.99(11)	O(2)-H2(O2)	0.78(12)
Bond angle	ϕ/°		ϕ/°
C(1)-C(2)-H1(C2)	108(3)	C(3)-C(2)-H1(C2)	119(3)
C(1)-C(2)-H2(C2)	113(3)	C(3)-C(2)-H2(C2)	122(3)
C(2)-C(3)-H(C3)	121(3)	C(4)-C(3)-H(C3)	112(3)
C(3)-C(4)-H1(C4)	107(3)	C(5)-C(4)-H1(C4)	106(3)
C(3)-C(4)-H2(C4)	109(3)	C(5)-C(4)-H2(C4)	122(3)
C(6)-C(7)-H(C7)	117(3)	C(8)-C(7)-H(C7)	115(3)
C(7)-C(8)-H(C8)	115(2)	C(9)-C(8)-H(C8)	122(3)
C(8)-C(9)-H(C9)	117(2)	C(10)-C(9)-H(C9)	111(2)
C(9)-C(10)-H1(C10)	111(3)	C(9)-C(10)-H2(C10)	106(3)
C(9)-C(10)-H3(C10)	102(3)	C(1)-C(11)-H1(C11)	109(3)
C(1)-C(11)-H2(C11)	108(3)	C(1)-C(11)-H3(C11)	102(3)
C(1)-C(12)-H1(C12)	111(3)	C(1)-C(12)-H2(C12)	108(4)
C(1)-C(12)-H3(C12)	97(3)	C(5)-C(13)-H1(C13)	118(3)
C(5)-C(13)-H2(C13)	105(3)	C(5)-C(13)-H3(C13)	117(3)
C(15)-C(16)-H(C16)	109(3)	C(17)-C(16)-H(C16)	130(3)
C(16)-C(17)-H(C17)	124(3)	C(18)-C(17)-H(C17)	117(3)
C(18)-C(19)-H(C19)	126(3)	C(20)-C(19)-H(C19)	115(3)
C(19)-C(20)-H(C20)	120(3)	C(15)-C(20)-H(C20)	115(3)
C(5)-O(2)-H1(O2)	111(7)	C(5)-O(2)-H2(O2)	120(8)



(a) (b)

Fig. 3. Newmann projections showing the conformations about (a) the C(6)–C(5) and (b) C(6)–C(1) bonds.

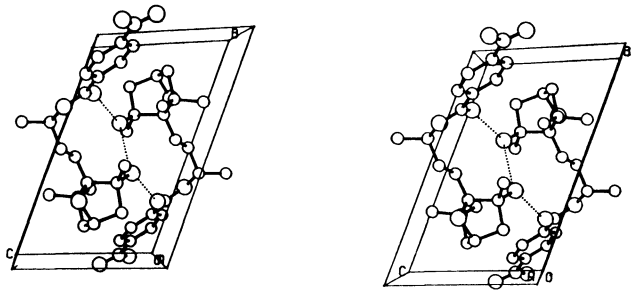


Fig. 4. A stereodrawing of the molecular packing viewed along the a axis.
Hydrogen bondings are shown by dotted lines.

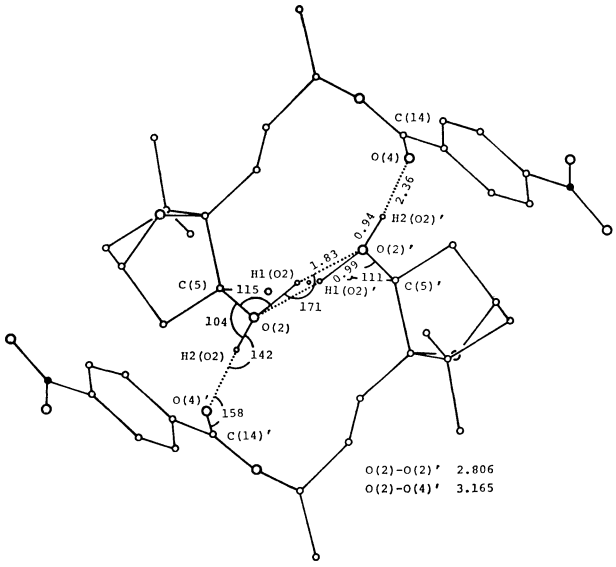


Fig. 5. Interatomic distances and angles associated with the hydrogen bondings.

TABLE 4. MOLECULAR GEOMETRY

(1) Least-squares planes defined by atomic positions and deviations (d/Å) of the atoms[a)]

Plane (1): C(1), C(2), C(3), and C(6)

$-0.3384X+0.3931Y-0.8550Z+4.895=0$

C(1) −0.009(17) C(2) 0.012(17) C(3) −0.010(17) C(6) 0.005(16) O(1)[b)] 0.80(2)

Plane (2): C(3), O(1), and C(6)

$-0.5501X-0.5404Y+0.6366Z+1.017=0$

C(1)[b)] 1.25(4) C(2)[b)] 1.21(4) C(4)[b)] −1.32(4) C(5)[b)] −1.39(4)

Plane (3): C(3), C(4), C(5), and C(6)

$0.9635X+0.1519Y+0.2203Z-6.324=0$

C(3) 0.031(12) C(4) −0.051(12) C(5) 0.027(11) C(6) −0.017(11) O(1)[b)] 0.86(1)

Plane (4): C(6), C(7), C(8), and C(9)

$-0.4797X-0.5867Y+0.6525Z+0.690=0$

C(6) −0.003(30) C(7) 0.004(30) C(8) 0.003(30) C(9) −0.003(30) C(3)[b)] 0.10(3)
C(10)[b)] 1.01(3) O(1)[b)] 0.12(3)

Plane (5): C(15), C(16), C(17), C(18), C(19), and C(20)

$-0.3228X+0.5584Y+0.7642Z-6.412=0$

C(15) 0.001(32) C(16) −0.003(32) C(17) 0.001(32) C(18) 0.004(32)
C(19) −0.005(32) C(20) 0.003(32) C(14)[b)] 0.09(3) O(3)[b)] −0.02(3)
O(4)[b)] 0.22(3) N[b)] 0.02(3) O(5)[b)] 0.12(3) O(6)[b)] −0.10(3)

(2) Dihedral angles (ϕ/°) between the planes

(1) and (2) 124.8(4) (1) and (3) 117.0(3) (1) and (4) 128.8(4) (2) and (3) 118.2(4)
(2) and (4) 4.9(6) (4) and (5) 71.1(3) (3) and (4) 114.0(4)

(3) Torsion angles

	ϕ/°		ϕ/°
C(6)-C(1)-C(2)-C(3)	1.7(6)	C(1)-C(2)-C(3)-C(4)	−75.4(6)
C(2)-C(3)-C(4)-C(5)	79.0(6)	C(3)-C(4)-C(5)-C(6)	−5.9(6)
C(4)-C(5)-C(6)-C(1)	−65.6(5)	C(5)-C(6)-C(1)-C(2)	68.8(5)
C(3)-O(1)-C(6)-C(1)	55.5(4)	C(3)-O(1)-C(6)-C(5)	−61.6(4)
C(3)-O(1)-C(6)-C(7)	178.8(4)	C(8)-C(9)-O(3)-C(14)	91.3(5)
C(10)-C(9)-O(3)-C(14)	−146.5(5)	C(8)-C(7)-C(6)-O(1)	5.5(7)
C(8)-C(7)-C(6)-C(1)	121.4(6)	C(8)-C(7)-C(6)-C(5)	−104.4(6)
C(7)-C(6)-C(1)-C(11)	−44.2(6)	C(7)-C(6)-C(1)-C(12)	78.8(6)
C(7)-C(6)-C(5)-C(13)	41.5(6)	C(7)-C(6)-C(5)-O(2)	−78.8(6)
C(6)-O(1)-C(3)-C(2)	−55.7(5)	C(6)-O(1)-C(3)-C(4)	59.1(5)
C(6)-C(7)-C(8)-C(9)	179.4(4)	C(7)-C(8)-C(9)-C(10)	132.9(5)
C(7)-C(8)-C(9)-O(3)	−110.0(5)	C(9)-O(3)-C(14)-O(4)	−1.2(9)
C(16)-C(15)-C(14)-O(3)	−8.2(8)	C(20)-C(15)-C(14)-O(4)	−3.2(9)
C(17)-C(18)-N-O(5)	−4.8(9)	C(19)-C(18)-N-O(6)	−6.4(9)

a) X, Y, and Z are coordinates expressed by the following equation

$$\begin{pmatrix} X \\ Y \\ Z \end{pmatrix} = \begin{pmatrix} a & b\cos\gamma & c\cos\beta \\ 0 & b\sin\gamma & -c\cos\alpha^*\sin\beta \\ 0 & 0 & c\sin\alpha^*\sin\beta \end{pmatrix} \begin{pmatrix} x \\ y \\ z \end{pmatrix}.$$

b) Atoms not included in the calculation of the plane.

distances (1.463 Å and 1.435 Å) and C(3)–O(1)–C(6) angle (96.3°) compare well with the values 1.443 Å, 1.452 Å and 96.2° for a toxisterol epoxide[8)] and the values 1.448 Å, 1.459 Å and 97.0° for triterpenoid baccharis oxide.[9)] The C(7)–C(8) double bond length of 1.326 Å and the two neighboring C(sp^2)–C(sp^3) bond lengths of 1.480 Å and 1.481 Å are also reasonable. All bond lengths and angles in the *p*-nitrobenzoate moiety are normal.

The molecular arrangement of the crystal is shown in Fig. 4. The molecules are placed in pairs around a center of symmetry, connected by two kinds of hydrogen bonds. As shown in Fig. 5, the final difference Fourier synthesis phased by all the atoms except H(O2) atom gave two peaks (H1(O2) and H2(O2)) at the positions expected for the H(O2) atom. From the facts that the electron density map shows heights of 0.4 and 0.3 e/Å^3 at the H1(O2) and H2(O2) peaks respectively and that the both O(2)–H1(O2) and O(2)–H2(O2) directions are favorable for hydrogen-bond formation, it was concluded that the two kinds of hydrogen bond exist at random; *i.e.*, when the O(2)H hydroxyl group donates its proton to the O(2)′ atom of the molecule connected by the crystallographic center of symmetry at (1/2, 1/2, 1/2), the hydrogen bond O(2)′–H2(O2)′···O(4) is formed, while when the O(2)H group donates its proton to the O(4)′ atom, the O(2)′–H1(O2)′···O(2) hydrogen bond is formed. As a result of the random distribution of these hydrogen bonds, the crystal is kept centrosym-

Table 5. Intermolecular distances shorter than 3.5 Å

From the unit (x, y, z) to the unit $(-x, -y, -z)$

From	To	Distance	Translation
C(7)	O(2)	3.418(6)	(1, 1, 1)
O(2)	O(2)	2.806(7)	(1, 1, 1) a)
O(2)	O(4)	3.165(6)	(1, 1, 1) a)
O(4)	O(5)	3.371(9)	(2, 1, 1)
O(19)	O(6)	3.383(8)	(2, 2, 1)
C(16)	O(1)	3.326(7)	(2, 1, 2)
C(15)	C(19)	3.453(8)	(2, 2, 2)
C(18)	O(4)	3.496(8)	(2, 2, 2)
O(4)	O(5)	3.489(7)	(2, 2, 2)
O(4)	O(6)	3.486(7)	(2, 2, 2)
N	O(4)	3.228(7)	(2, 2, 2)

a) Hydrogen bonding.

metric. The intermolecular distances less than 3.5 Å are listed in Table 5. Excepting the hydrogen-bond interactions, there are no closer intermolecular contacts than van der Waals contacts.

This X-ray crystallographic study showed the relative configuration of **1** to be (±)-(1*R*,2*R*,5*S*)-2,5-epoxy-2-[(1*E*,3*S*)-3-hydroxy-1-butenyl]-1,3,3-trimethyl-1-cyclohexanol.

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