

The Absolute Configuration of Hyperforin, an Antibiotic from *Hypericum perforatum* L., Based on the Crystal Structure Determination of its *p*-Bromobenzoate Ester

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The antibiotic properties of the antibacterial substances known to be present in species of the genus *Hypericum* (Hypericaceae (=Guttiferace)),¹ are well established.²⁻⁴ Extracts from this plant have been used to preserve food³ and to treat infections.⁵ One active constituent designated hyperforin, was isolated and characterized in 1971.⁵ The absolute configuration was suggested in 1975-1976.^{6,7} A forthcoming report⁸ presents arguments suggesting that a recent crystal structure determination of the 3,5-dinitrobenzoate ester⁹ is in contradiction with the proposed absolute configuration. In order to obtain direct evidence for the absolute stereochemistry of hyperforin, a single crystal structure analysis of its *p*-bromobenzoate ester has been carried out.

The crystal data for C₄₂H₅₅BrO₅ are: $a=11.692(4)$ Å, $b=16.253(9)$ Å, $c=10.233(4)$ Å, $\beta=102.60(3)^\circ$, $Z=2$, space group $P2_1$, $D_x=1.26$ g cm⁻³, $D_m=1.23$ g cm⁻³, $\mu=1.19$ mm⁻¹ (MoK α). Data were collected on an automatic four-circle

Table 1. Final fractional coordinates with estimated standard deviations for non-hydrogen atoms.

ATOM	X	Y	Z
BR	.88298(3)	.73992(3)	.35632(4)
O1	.30912(23)	.82176(18)	1.03682(27)
O2	.03362(23)	.79546(17)	.70619(29)
O3	.00456(26)	.81537(20)	.99374(33)
O4	.42445(19)	.73957(23)	.66286(23)
O5	.32359(26)	.78297(21)	.45931(30)
C1	.27436(33)	.81595(24)	.91791(42)
C2	.14532(32)	.80554(25)	.85188(39)
C3	.10215(33)	.89247(25)	.78444(41)
C4	.18723(40)	.91151(28)	.67978(47)
C5	.31157(35)	.91913(27)	.74314(41)
C6	.35219(32)	.82702(25)	.81778(40)
C7	.32929(33)	.75535(26)	.72031(37)
C8	.23141(35)	.71044(24)	.69103(38)
C9	.12992(30)	.73661(33)	.74551(35)
C10	.08112(36)	.77555(27)	.95959(44)
C11	.11718(38)	.69156(28)	1.02427(45)
C12	.01238(44)	.62919(33)	.98316(61)
C13	.14813(41)	.71132(30)	1.17823(46)
C14	.12316(35)	.95838(26)	.89531(44)
C15	-.02839(33)	.88609(26)	.71176(41)
C16	-.10554(36)	.96294(27)	.71776(45)
C17	-.22187(38)	.95864(29)	.62096(47)
C18	-.32612(37)	.98188(28)	.63843(50)
C19	-.34757(41)	1.02320(32)	.76146(56)
C20	-.43221(40)	.97645(33)	.52581(54)
C21	.14812(37)	.99321(27)	.60391(46)
C22	.21939(36)	1.00867(27)	.49993(46)
C23	.20059(40)	.97786(31)	.37733(51)
C24	.10129(44)	.92031(35)	.32300(54)
C25	.27923(46)	.99784(38)	.28336(52)
C26	.41332(36)	.75994(26)	.52909(40)
C27	.52675(31)	.74886(31)	.48859(36)
C28	.53084(38)	.76487(28)	.35631(43)
C29	.63689(38)	.76114(28)	.31785(43)
C30	.73733(30)	.74163(37)	.41035(38)
C31	.73523(34)	.72219(27)	.54204(40)
C32	.62886(33)	.72566(28)	.58042(38)
C33	.48241(34)	.83176(27)	.89123(42)
C34	.52832(32)	.75207(30)	.95466(38)
C35	.63667(34)	.72149(28)	.96931(40)
C36	.73521(36)	.76459(30)	.92698(46)
C37	.66799(40)	.63852(32)	1.03485(48)
C38	.21535(37)	.63382(28)	.60457(45)
C39	.18779(49)	.55995(30)	.68438(54)
C40	.26595(40)	.52024(28)	.77692(49)
C41	.23080(44)	.44791(31)	.85211(52)
C42	.39347(43)	.54219(32)	.81801(53)

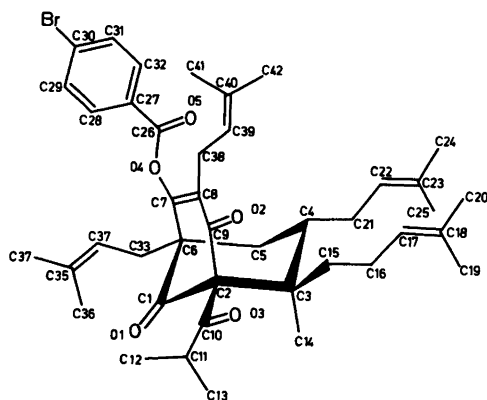


Fig. 1. Schematic drawing of the molecule showing the numbering of atoms.

diffractometer at *ca.* -150°C by the ω -scan technique ($2\theta_{\text{max}}=50^\circ$, MoK α -radiation). 6686 reflections (Friedel equivalents included) were collected. With an observed-unobserved cutoff at $2.5\sigma(I)$, 5661 reflections were regarded as observed. The intensities were corrected for absorption (crystal size $0.3\times 0.2\times 0.1$ mm). The minimum and maximum transmission factors were 0.75 and 0.90, respectively. The phase problem was solved by direct methods.¹¹ Without taking into account anomalous dispersion, full-matrix least-squares refinement^{12,*} converged at

* All programs used (except those for phase determination) are included in this reference.

Table 2. Bond distances and angles with estimated standard deviations.

DISTANCE		(Å)	DISTANCE		(Å)
BR - C30	1.902(3)		O1 - C1	1.198(5)	
O2 - C9	1.220(5)		O3 - C10	1.206(5)	
O4 - C7	1.391(4)		O4 - C26	1.383(5)	
O5 - C26	1.198(5)		C1 - C2	1.522(5)	
C1 - C6	1.521(5)		C2 - C3	1.605(6)	
C2 - C9	1.545(6)		C2 - C10	1.550(6)	
C3 - C4	1.582(6)		C3 - C14	1.540(6)	
C3 - C15	1.549(5)		C4 - C5	1.532(6)	
C4 - C21	1.543(6)		C5 - C6	1.558(6)	
C6 - C7	1.519(6)		C6 - C33	1.547(6)	
C7 - C8	1.335(6)		C8 - C9	1.479(5)	
C8 - C38	1.515(6)		C10 - C11	1.538(6)	
C11 - C12	1.525(7)		C11 - C13	1.546(7)	
C15 - C16	1.550(6)		C16 - C17	1.501(6)	
C17 - C18	1.332(6)		C18 - C19	1.496(7)	
C18 - C20	1.501(7)		C21 - C22	1.509(6)	
C22 - C23	1.324(7)		C23 - C24	1.500(7)	
C23 - C25	1.514(7)		C26 - C27	1.483(5)	
C27 - C28	1.390(6)		C27 - C32	1.400(5)	
C28 - C29	1.382(6)		C29 - C30	1.375(6)	
C30 - C31	1.390(6)		C31 - C32	1.385(5)	
C33 - C34	1.495(6)		C34 - C35	1.338(5)	
C35 - C36	1.491(6)		C35 - C37	1.515(7)	
C38 - C39	1.537(7)		C39 - C40	1.318(7)	
C40 - C41	1.516(7)		C40 - C42	1.502(6)	
ANGLE		(°)	ANGLE		(°)
C7 - O4 - C26	117.7(3)		O1 - C1 - C2	122.8(4)	
O1 - C1 - C6	123.8(4)		C2 - C1 - C6	113.2(3)	
C1 - C2 - C3	106.3(3)		C1 - C2 - C9	110.2(3)	
C1 - C2 - C10	108.3(3)		C3 - C2 - C9	111.0(3)	
C3 - C2 - C10	115.2(3)		C9 - C2 - C10	105.8(3)	
C2 - C3 - C4	106.8(3)		C2 - C3 - C14	108.1(3)	
C2 - C3 - C15	109.4(3)		C4 - C3 - C14	109.9(3)	
C4 - C3 - C15	110.0(3)		C14 - C3 - C15	112.5(3)	
C3 - C4 - C5	112.4(4)		C3 - C4 - C21	113.3(4)	
C5 - C4 - C21	110.3(4)		C4 - C5 - C6	113.6(3)	
C1 - C6 - C5	105.6(3)		C1 - C6 - C7	107.8(3)	
C1 - C6 - C33	110.4(3)		C5 - C6 - C7	110.1(3)	
C5 - C6 - C33	111.0(3)		C7 - C6 - C33	111.7(3)	
O4 - C7 - C6	112.1(3)		O4 - C7 - C8	122.0(4)	
C6 - C7 - C8	125.9(3)		C7 - C8 - C9	118.5(4)	
C7 - C8 - C38	124.8(4)		C9 - C8 - C38	116.7(4)	
O2 - C9 - C2	119.4(3)		O2 - C9 - C8	121.0(4)	
C2 - C9 - C8	119.6(3)		O3 - C10 - C2	122.8(4)	
O3 - C10 - C11	120.5(4)		C2 - C10 - C11	116.7(4)	
C10 - C11 - C12	110.3(4)		C10 - C11 - C13	109.2(4)	
C12 - C11 - C13	110.2(4)		C3 - C15 - C16	116.6(3)	
C15 - C16 - C17	111.9(4)		C16 - C17 - C18	128.0(4)	
C17 - C18 - C19	125.2(4)		C17 - C18 - C20	121.4(5)	
C19 - C18 - C20	114.2(4)		C4 - C21 - C22	112.8(4)	
C21 - C22 - C23	127.0(4)		C22 - C23 - C24	122.8(5)	
C22 - C23 - C25	121.7(5)		C24 - C23 - C25	115.4(5)	
O4 - C26 - O5	123.0(4)		O4 - C26 - C27	110.7(3)	
O5 - C26 - C27	126.2(4)		C26 - C27 - C28	118.3(4)	
C26 - C27 - C32	121.7(3)		C28 - C27 - C32	119.9(3)	
C27 - C28 - C29	119.5(4)		C28 - C29 - C30	119.9(4)	
BR - C30 - C29	119.3(3)		BR - C30 - C31	118.9(3)	
C29 - C30 - C31	121.8(3)		C30 - C31 - C32	118.2(4)	
C27 - C32 - C31	120.5(3)		C6 - C33 - C34	113.0(3)	
C33 - C34 - C35	127.7(4)		C34 - C35 - C36	124.4(4)	
C34 - C35 - C37	120.8(4)		C36 - C35 - C37	114.8(4)	
C8 - C38 - C39	110.7(4)		C38 - C39 - C40	124.3(5)	
C39 - C40 - C41	121.9(4)		C39 - C40 - C42	125.5(5)	
C41 - C40 - C42	113.6(4)				

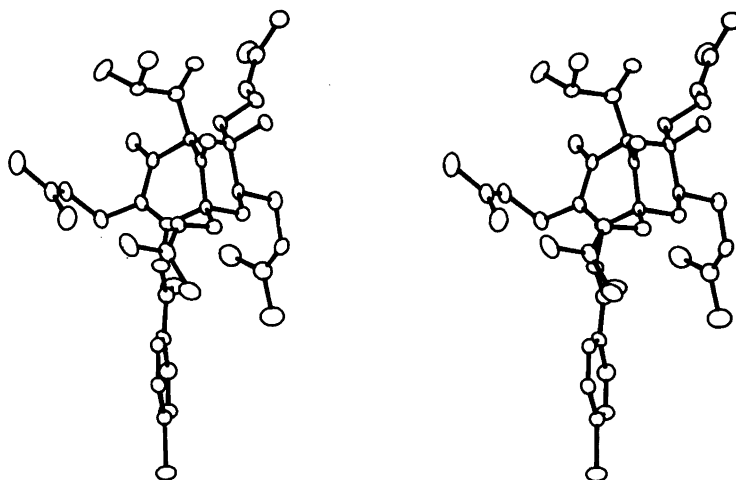


Fig. 2. Stereoscopic view of the molecule.

$R \sim 10\%$. By introducing anomalous scattering factors for Br with $+\Delta f'' = 2.456$, further refinement led to $R = 7.9\%$ ($R_w = 9.0\%$). When now changing the sign to $-\Delta f''$, the values dropped to $R = 4.7\%$ and $R_w = 4.9\%$, respectively. The final values were $R = 4.5\%$ and $R_w = 4.7\%$. The methyl hydrogen atoms were localized in a difference Fourier map while the positions of the other hydrogen atoms were calculated. Anisotropic temperature factors were introduced for all non-hydrogen atoms. The maximum r.m.s. amplitudes range from 0.15 to 0.26 Å. Weights in least squares were obtained from the standard deviations in intensities, $\sigma(I)$, taken as

$$\sigma(I) = [C_T + (0.02C_N)^2]^{1/2}$$

where C_T is the total number of counts, and C_N the net count. Only positional parameters for hydrogen atoms were refined.

Final fractional atomic coordinates for non-hydrogen atoms are given in Table 1. Bond distances and angles may be found in Table 2. Fig. 1 is a schematic drawing of the molecule showing the numbering of atoms. A stereoscopic view of the molecule is presented in Fig. 2. It may be noticed that the bond distances C2–C3 (1.605 Å) and C3–C4 (1.582 Å) are unusually long. However, the corresponding values for the 3,5-dinitrobenzoate ester⁹ were also long (1.58 Å and 1.57 Å). The environment of the bond C8–C14 in the crystals of 3 β ,28-diacetoxy-18 β ,19 β -epoxylupane¹⁰ resembles that of C2–C3 in the present molecule. C8–C14 was found to be 1.605 Å. All other bond distances and angles have normal values within estimated limits of error. It may be pointed out that the difference between the earlier suggested absolute

configuration^{6,7} and the present one, is that the stereochemistry at the chiral centres C2 and C8 is opposite.

Lists of observed and calculated structure factors as well as the temperature factors are obtainable from Per Groth.

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