From the out-of-plane displacements of the acenaphthene nuclei, it is clear that the twisting modes of the ethylene bridges, C(1*A*)–C(2*A*) and C(1*B*)–C(2*B*), differ from those of 5,6-dichloro-, 5-bromo-6-chloro-, and 5,6-diphenylacenaphthenes (Avoyan & Struchkov, 1961, 1964; Clough, Kung, Marsh & Roberts, 1976). The bond angles of C(6) also differ from those of these acenaphthene *peri* derivatives, in which the angles *X*–C(5)–C(10) and *X*–C(6)–C(10) are expanded, where *X* is a carbon or halogen atom of the *peri* substituent. In the present structures, however, O(3)–C(6)–C(10) is smaller than O(3)–C(6)–C(7). This may be due to the intramolecular hydrogen bonds mentioned above. C(7)–C(6)–C(10), however, is larger than C(4)–C(5)–C(10). This can be understood by the difference in electronegativities between the substituted atoms, O(3) and C(13), in terms of the valence-shell electron-pair repulsion theory (Domenicano, Vaciago & Coulson, 1975).

Interpretation of the unusual ^{1}H NMR spectra of the present compound (Tanaka & Kasai, to be published) is now possible on the basis of the anomalous configurations causing the shortenings of some H–H distances shown in Figs. 2 and 3.

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Structure of Trichostatin A, a Primary Hydroxamate Antibiotic

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Abstract. $C_{17}H_{22}N_2O_3$, M_r = 302·4, orthorhombic, $P2_12_12_1$, $Z = 8$; a = 10·446 (3), b = 41·277 (16), c = 7·669 (2) Å, V = 3307 (2) Å^3 at 138 (2) K; a = 10·499 (4), b = 41·528 (24), c = 7·753 (2) Å, V = 3380 (3) Å^3 at 295 (1) K; Cu $K\alpha_1$ radiation, λ = 1·5405 Å; μ(Cu $K\alpha$) = 0·67 mm^{-1}; D_c = 1·188, D_m = 1·12 (1) Mg m^{-3} [295 (1) K]; recrystallized from ethyl acetate–methanol. Trichostatin A is a primary hydroxamic acid and antifungal antibiotic produced by *Streptomyces hygroscopicus* Y-50. The structure was determined from 3886 intensity measurements at 138 (2) K by direct methods and difference Fourier syntheses, and refined to an R factor of 0·097 for 3284 data (0·117 for all reflections). The two molecules in the asymmetric unit are closely similar; the unsaturated side chain is all-*trans* and exhibits a significant degree of in-plane bending, while the intermolecular hydrogen-bonded hydroxamate group is planar *cis*.

Introduction. The crystal structure and absolute configuration of naturally occurring biologically active hydroxamic acids [R_1–C(=O)–N(–OH)–R_2], both linear and cyclic, and their ferric chelates, are of interest because of their ability to sequester selectively and facilitate the transport of ferric ions across cell membranes. Trichostatin A is a member of a group of relatively lipophilic hydroxamic acids isolated and identified from the mycelia of *Streptomyces hygroscopicus* Y-50 (Tsuji, Kobayashi, Nagashima, Wakisaka & Koizumi, 1976; Tsuji & Kobayashi, 1978). It is a primary hydroxamic acid (R_2 = H), coordinates ferric ion as a 3:1 complex, and exhibits anti-*Trichophyton* activity. The antibiotic activity of the hydroxamic acid diminishes substantially (by a factor of 4 or 8) as either the tris ferrate(III) complex or as the β-glycopyranosyl derivative. Its ability to act as a ferric ionophore (siderophore) in *S. hygroscopicus* has not yet been confirmed. The present communication confirms the chemical structure postulated by Tsuji *et al.* (1976).

The title compound was obtained as a gift from Dr Naoki Tsuji, Shionogi Research Laboratory, Shionogi

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& Co. Ltd, Osaka, Japan. Long, colorless boat-shaped crystals were grown by slow evaporation from an ethyl acetate–methanol solution. A crystal was selected and used for unit-cell and space-group determinations, and intensity-data collection, all of which were carried out on an Enraf–Nonius CAD-4 automatic diffractometer equipped with a low-temperature nitrogen cooling device. Although the crystal was large (0·77 × 0·15 × 0·09 mm), and proved to be the best among a number examined, it did have a large mosaic (2·0°). This possibly caused errors in the data and no doubt affected the quality of the refined structure. The unit-cell dimensions were determined from a least-squares fit of the 2θ values of 48 reflections measured at room (295 K) and at low [138 (2) K] temperature using Cu $K\alpha_1$ radiation (λ = 1·54051 Å). The noncentrosymmetric orthorhombic space group, $P2_12_12_1$, with two molecules per asymmetric unit, was uniquely determined from the systematic absences: $h00$, for $h = 2n + 1$; $0k0$, for $k = 2n + 1$; and $00l$, for $l = 2n + 1$. The density was measured by the flotation method.

The intensities of all 3886 unique reflections with $2\theta \le 150°$ were measured with Cu $K\bar{\alpha}$ radiation (λ = 1·5418 Å) using the θ–2θ scan technique; the scan angle was calculated from $\theta = (0{\cdot}9 + 0{\cdot}14 \tan\theta)°$, and the variable aperture width was computed as $(4{\cdot}0 + 0{\cdot}86 \tan\theta)$ mm. Each reflection was scanned for 60 s, with $\frac{2}{3}$ of this period dedicated to peak (P) counting, and $\frac{1}{6}$ each for low-θ (L) and high-θ (H) background enumeration. The unscaled intensities were computed as $I = P - 2{\cdot}0(L + H)$. Three intensity monitor reflections were measured after every 75 min of X-ray exposure, and used for data normalization. Three orientation-control reflections were centered after every 200 measurements; a new orientation matrix was automatically computed from a list of 15 reflections if the angular change in θ, χ, or φ was greater than 0·1°. Of the 3886 independent data, 481 reflections were considered unobserved [$I < 2{\cdot}0\ \sigma(I)$]. The data were corrected for Lorentz and polarization effects, but were not corrected for absorption.

The structure was solved by direct methods using the program *MULTAN* 78 (Main, Woolfson, Lessinger, Germain & Declercq, 1978) and successive difference Fourier syntheses. The positions of all nonhydrogen atoms were refined, isotropically then anisotropically, using a block-diagonal least-squares program (Ahmed, 1966) in which the quantity $\sum W_F(|kF_o| - |F_c|)^2$ was minimized. The H atoms (20 of 44) were located in a difference Fourier map and refined isotropically. A final difference Fourier map revealed 18 significant peaks (~0·3–0·6 e Å^{-3}) at positions in the proximity of the eight methyl C atoms. Each structure amplitude was assigned a weight, $W_F(=1/\sigma_F^2)$, where σ_F^2 was obtained from counting statistics (Ealick, van der Helm & Weinheimer, 1975). The scattering factors for the C, N and O atoms were taken from *International Tables for X-ray Crystallography* (1974), and those for the H atoms from Stewart, Davidson & Simpson (1965). The

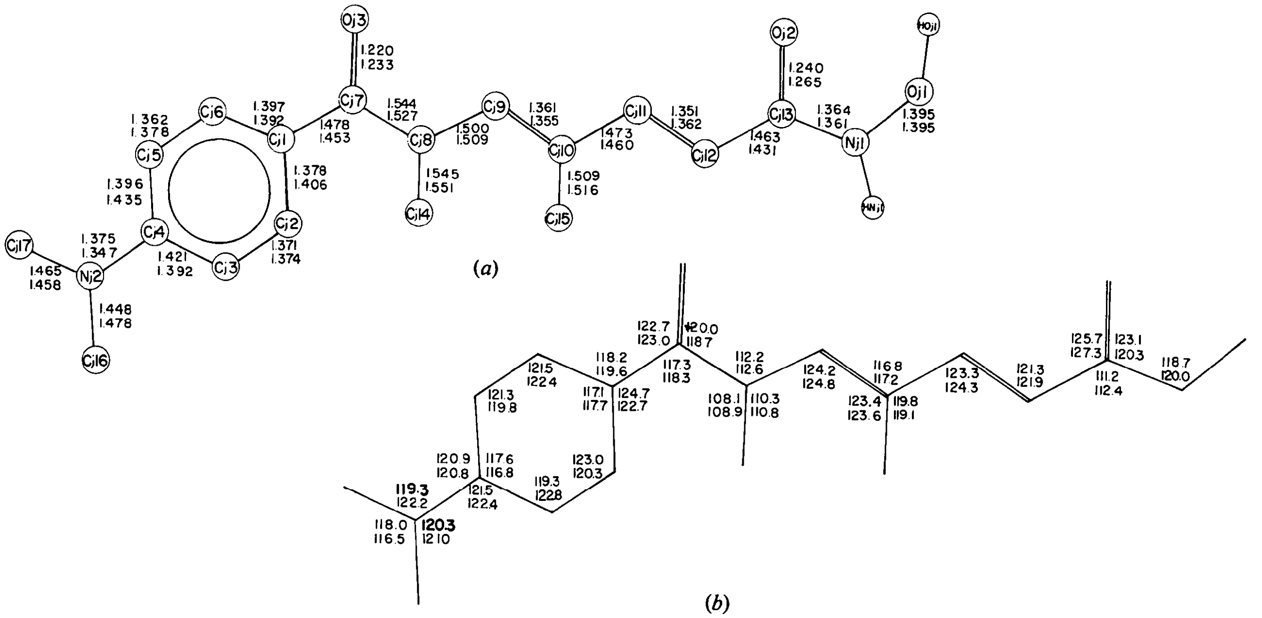

Fig. 1. (a) Atom numbering scheme (i = 1,2) and bond distances (Å) in Trichostatin A, where the upper and lower values are for molecules 1 and 2, respectively. The e.s.d.'s for both molecules, as mean (range), are: C—C, 0·011 (0·010–0·012); C—O, 0·009, C—N, 0·010 (0·009–0·011); and N—O, 0·008 Å. (b) Bond angles (°), where upper and lower values are for molecules 1 and 2, respectively. The e.s.d.'s for both molecules are in the range 0·6–0·7°.

Table 1. *Atomic coordinates and U_{eq} for the non-hydrogen atoms in Trichostatin A (two molecules per asymmetric unit)*

$U_{eq} = (\frac{1}{6}\pi^2)\sum_i\sum_j\beta_{ij}\mathbf{a}_i.\mathbf{a}_j$. Standard deviations of the last significant figure are given in parentheses.

	$x\,(\times10^4)$	$y\,(\times10^5)$	$z\,(\times10^4)$	U_{eq} (Å^2)
O(11)	6260 (5)	10778 (13)	−9358 (7)	0·034 (3)
O(12)	5457 (6)	11796 (11)	−6031 (7)	0·036 (3)
O(13)	6201 (5)	1426 (11)	1114 (7)	0·028 (3)
N(11)	6025 (6)	8251 (15)	−8195 (8)	0·030 (3)
N(12)	5415 (7)	−13415 (15)	3122 (9)	0·036 (4)
C(11)	5234 (7)	−3715 (18)	1514 (10)	0·028 (4)
C(12)	4149 (7)	−5607 (19)	1596 (11)	0·033 (4)
C(13)	4166 (7)	−8782 (19)	2119 (10)	0·032 (4)
C(14)	5348 (8)	−10234 (18)	2598 (10)	0·031 (4)
C(15)	6441 (7)	−8290 (19)	2559 (10)	0·031 (4)
C(16)	6379 (8)	−5117 (19)	2080 (11)	0·033 (4)
C(17)	5257 (7)	−288 (16)	958 (9)	0·024 (3)
C(18)	4029 (7)	1084 (18)	115 (10)	0·026 (4)
C(19)	4311 (7)	3745 (16)	−1160 (10)	0·027 (4)
C(110)	4868 (6)	3278 (16)	−2745 (9)	0·024 (3)
C(111)	5029 (7)	6163 (18)	−3855 (10)	0·029 (4)
C(112)	5552 (8)	6064 (18)	−5465 (10)	0·029 (4)
C(113)	5664 (7)	8988 (16)	−6533 (9)	0·027 (4)
C(114)	3151 (8)	2343 (22)	1588 (12)	0·040 (4)
C(115)	5323 (8)	18 (19)	−3383 (11)	0·032 (4)
C(117)	6662 (9)	−15035 (22)	3176 (13)	0·045 (5)
C(116)	4277 (9)	−15416 (20)	3131 (13)	0·044 (5)
O(21)	3461 (5)	13803 (13)	−4271 (7)	0·033 (3)
O(22)	4172 (5)	12678 (13)	−937 (7)	0·034 (3)
O(23)	3808 (5)	23431 (11)	6214 (7)	0·029 (3)
N(21)	3801 (6)	16286 (15)	−3128 (8)	0·031 (3)
N(22)	5294 (8)	38215 (16)	7562 (11)	0·046 (4)
C(21)	4980 (7)	28300 (18)	6498 (10)	0·028 (4)
C(22)	6173 (7)	29875 (19)	6453 (10)	0·032 (4)
C(23)	6266 (8)	33099 (19)	6880 (10)	0·033 (4)
C(24)	5205 (8)	35004 (19)	7272 (10)	0·032 (4)
C(25)	3987 (8)	33399 (19)	7313 (11)	0·033 (4)
C(26)	3916 (7)	30119 (19)	6989 (10)	0·032 (4)
C(27)	4814 (7)	24934 (18)	5989 (10)	0·026 (4)
C(28)	5956 (8)	23157 (18)	5193 (10)	0·030 (4)
C(29)	5558 (7)	20556 (18)	3922 (10)	0·029 (4)
C(210)	5101 (8)	21112 (19)	2295 (10)	0·033 (4)
C(211)	4777 (7)	18287 (18)	1237 (10)	0·029 (4)
C(212)	4332 (8)	18442 (19)	−430 (10)	0·030 (4)
C(213)	4094 (7)	15591 (19)	−1440 (9)	0·029 (4)
C(214)	6780 (8)	21707 (20)	6684 (11)	0·035 (4)
C(215)	4927 (9)	24468 (19)	1528 (11)	0·043 (5)
C(216)	6555 (9)	39828 (20)	7676 (13)	0·046 (5)
C(217)	4173 (10)	40320 (22)	7593 (14)	0·052 (6)

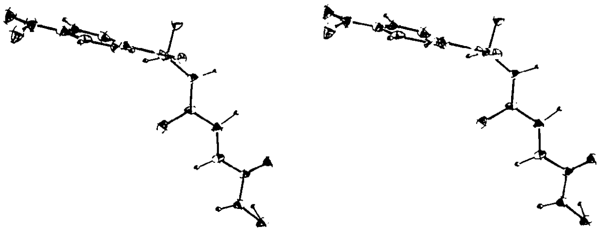

Fig. 2. Stereoscopic view of a single molecule (1) of Trichostatin A.

final R factor $[R = |\sum(|kF_o| - |F_c|)|/\sum|kF_o|]$ was 0·097 for 3284 data, 0·117 for all 3886 reflections and the goodness-of-fit 4·59. An analysis of the calculated and observed structure factors showed no significant variation of $W_F\Delta F^2$ with either $|F_o|$ or $\sin\theta/\lambda$. The final atomic coordinates for the nonhydrogen atoms are in Table 1.* Bond distances, bond angles and torsion angles are given in Fig. 1 and Table 2, respectively; a stereoscopic view of a single molecule (1) is given in Fig. 2.

Discussion. The two molecules in the asymmetric unit are not significantly different. The quality of the crystal did not allow a determination of the absolute configuration of the compound. The relative configuration for both independent molecules is the same. From the bond distances and angles shown in Figs. 1 and 2, it can be seen that the aromatic ring has significant quinoid character.

The dimethylamino group is not quite coplanar with the planar benzoyl ring ($\bar{\sigma}_{\rm r.m.s.}$, 0·18 Å); the out-of-plane deformation of the bonds about N(i2) (i = 1,2) (χ_N, after Winkler & Dunitz, 1971) is 17·8 (9) and 6·7 (10)°, respectively. The conformation of the conjugated double-bond system of the planar side chain

Table 2. *Torsion angles* (°) *in Trichostatin A*

The e.s.d.'s for both molecules are in the range 0·7–1·2°.

	$i=1$	$i=2$		$i=1$	$i=2$		$i=1$	$i=2$
C(i2)–C(i1)–C(i7)–C(i8)	−11	−7	C(i12)–C(i13)–N(i1)–O(i1)	−176	−176	C(i14)–C(i8)–C(i9)–C(i10)	−168	−164
C(i1)–C(i7)–C(i8)–C(i9)	−151	−150	O(i2)–C(i13)–N(i1)–O(i1)	5	6	C(i8)–C(i9)–C(i10)–C(i15)	−3	0
C(i7)–C(i8)–C(i9)–C(i10)	71	74	O(i3)–C(i7)–C(i1)–C(i6)	−6	−11	C(i15)–C(i10)–C(i11)–C(i12)	1	1
C(i8)–C(i9)–C(i10)–C(i11)	178	179	O(i3)–C(i7)–C(i8)–C(i9)	28	32	C(i11)–C(i12)–C(i13)–O(i2)	9	5
C(i9)–C(i10)–C(i11)–C(i12)	−179	−179	O(i3)–C(i7)–C(i8)–C(i14)	−94	−91	C(i3)–C(i4)–N(i2)–C(i16)	2	−7
C(i10)–C(i11)–C(i12)–C(i13)	179	177	C(i1)–C(i7)–C(i8)–C(i14)	87	87	C(i5)–C(i4)–N(i2)–C(i17)	−17	−12
C(i11)–C(i12)–C(i13)–N(i1)	−170	−173						

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* Lists of structure factors, anisotropic thermal parameters and H-atom coordinates have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 35705 (24 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

$\{\bar{\sigma}_{\text{r.m.s.}}$ [C(*i*8)—C(*i*13) (i = 1,2)], 0·02 Å$\}$ is *trans*; the side chain is bent out of the plane of the dimethylaminobenzoyl group by 73·6 and 76·5° for the two molecules. The bending of the side chain occurs primarily at the C(*i*8)—C(*i*9) and C(*i*9)—C(*i*10) bonds and is reflected in average torsion angles of 150 (1) and 73 (1)°, respectively. The C(*i*8)—C(*i*14) bond is approximately *trans* to C(*i*10)—C(*i*15) and nearly perpendicular to C(*i*7)—O(*i*3) [the mean torsion angle about O(*i*3)—C(*i*7)—C(*i*8)—C(*i*14) is −92 (1)°]. As a consequence of these nonbonding steric interactions, the conformation of the side chain is not strictly zigzag, but rather possesses a significant degree of in-plane bending (Δ = 9·7°, after Schenk, 1971) reminiscent of the in-plane bending observed in the crystal structures of vitamin A and its derivatives (Stam, 1972; Oberhänsli, Wagner & Isler, 1974). Also, a number of short (2·0 Å) internal H···H contacts arise from this sabre-like conformation.

This structure represents the first crystal structure determination of a natural primary hydroxamic acid, although the structures of several synthetic hydroxamates have been reported, including: aceto- (Bracher & Small, 1970), benzo- (*cf.* Göttlicher & Ochsenreiter, 1974), and salicyl- (Larsen, 1978), and the secondary hydroxamate *N*,*N'*-dihydroxy-*N*,*N'*-diisopropylhexanediamide (Smith & Raymond, 1980). The hydroxamate group assumes the planar *cis* conformation, *vis-à-vis* the more stable *trans* conformation, observed in the fourth structure, probably due to the presence of four intermolecular hydrogen bonds. The $\bar{\sigma}_{\text{r.m.s.}}$ deviation of the atoms C(*i*13), O(*i*2), N(*i*1) and O(*i*1) (i = 1,2) is 0·017 Å, with a mean torsion angle about the C(*i*13)—N(*i*1) bond of 6°. The average hydroxamate N—O and C—O lengths in Trichostatin A are the same as those observed in the synthetic hydroxamic acids, while the C—C and C—N distances are systematically shorter and longer, respectively, due to the conjugation of the hydroxamate group with the unsaturated side chain.

In the crystal structures, there are two strong intermolecular hydrogen bonds formed between the hydroxamate group of stacks of molecules related by a twofold screw axis. This results in a helical arrangement of molecules along the short *c* axis. These bonds are O(12)—O(21), 2·62 (1) Å, and O(22)—O(11)($x, y, z + 1$), 2·61 (1) Å. The H atoms [H(O*i*1) (i = 1,2)] are elongated along the line between the donor–acceptor O atoms, as reflected in the large isotropic thermal factors associated with these atoms. The H atoms H(N*i*1) of N(*i*1) lie in the plane of the hydroxamate group and are involved in intermolecular hydrogen bonds with the benzoyl O atom [O(*i*3) (i = 1,2) ($x, y, z - 1$)] of lengths 2·87 (1) and 2·99 (1) Å, respectively.

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