C6—C7—C8	130.7 (3)	C1—C20—C19	130.9 (2)
C2—C7—C8	108.7 (2)	C1—C20—C8	112.3 (2)
C7—C8—C20	102.3 (2)	C19—C20—C8	116.8 (2)

Data collection: Siemens *P3* software. Cell refinement: Siemens *P3* software. Data reduction: *XDISK* (Siemens, 1991). Program(s) used to solve structure: *SHELXTL* (Sheldrick, 1994). Program(s) used to refine structure: *SHELXTL*. Molecular graphics: *SHELXTL XP*. Software used to prepare material for publication: *SHELXTL XCIF*.

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: BK1209). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

References

Hitchcock, S. R., Situ, J. J., Covel, J. A., Olmstead, M. M. & Nantz, M. H. (1995). *Organometallics*, pp. 3732–3740.

Hoveyda, A. H. & Morken, J. P. (1993). *J. Org. Chem.* **58**, 4237–4244.

Sheldrick, G. M. (1994). *SHELXTL. Structure Determination Programs*. Version 5.03. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.

Siemens (1991). *XDISK. Data Reduction Program*. Version 3.11. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.

Willoughby, C. A. & Buchwald, S. L. (1994). *J. Am. Chem. Soc.* **116**, 11703–11714.

Acta Cryst. (1996). C**52**, 1525–1527

Hemiasterlin Methyl Ester†

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Abstract

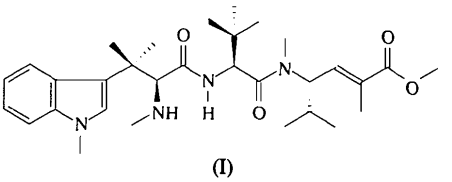
The structure of the tripeptide hemiasterlin methyl ester, $C_{31}H_{48}N_4O_4$, has been determined by X-ray analysis. The absolute configuration is based on the chiralities determined by other methods for two of the three chiral centers. Weak hydrogen bonding influences the solid-state conformation.

† IUPAC name: methyl 2,5-dimethyl-4-{2-[3-methyl-2-methylamino-3-(*N*-methylbenzo[*b*]pyrrol-3-yl)butanamido]-3,3-dimethyl-*N*-methylbutanamido}-2-hexenoate.

Comment

Marine sponges are a rich source of novel peptide metabolites that frequently exhibit potent biological activity (Fusetani & Matsunaga, 1993). We have recently reported the isolation of the tripeptides hemiasterlin, hemiasterlin A and hemiasterlin B, and the tetrapeptides criamide A and criamide B from the sponge *Cymbastela sp.* collected in Papua New Guinea (Coleman, de Silva, Kong, Andersen & Allen, 1996). One of these peptides, hemiasterlin, has been isolated previously from the marine sponge *Hemiasterella minor* collected in South Africa (Talpir, Benayahu, Kashman, Pannell & Schleyer, 1994) and a related compound, milnamide A, has been reported as being isolated from the sponge *Auletta c.f. constricta*, also collected in Papua New Guinea (Crews, Farias, Emrich & Keifer, 1994). The hemiasterlins and criamides exhibit potent *in vitro* inhibition of murine leukemia P388 and human solid-tumor cell lines and show promising *in vivo* activity against murine leukemia P388 in mice (Coleman *et al.*, 1995). Preliminary investigations indicate that the hemiasterlins are antimitotic agents that target cellular tubulin in a manner similar to the cytotoxic mechanisms of the well known anticancer drugs vincristine and taxol (Roberge, Anderson, Coleman & Andersen, 1995).

The cytotoxic properties of the hemiasterlins and criamides make them attractive targets for total synthesis. Any synthetic effort towards these cytotoxic peptides would benefit from knowledge of the absolute configurations of the component amino acids. Degradative analysis carried out as part of the structure elucidation of the hemiasterlins and criamides isolated from *Cymbastela sp.* showed that the *tert*-leucine, valine, *N*-methylhomovinylagous valine and arginine residues in these molecules all had the L configuration (Coleman *et al.*, 1995). Attempts to determine the configuration of the methylated tryptophan residues in the hemiasterlins and criamides by hydrolysis or circular dichorism analysis were unsuccessful. Fortunately, the methyl ester of hemiasterlin, (I), gave crystals suitable for X-ray diffraction analysis.



(I)

The results of this X-ray diffraction analysis, which are presented below, show that the tetramethylated tryptophan residue in hemiasterlin also has the L configuration. The molecular conformation in the solid state is stabilized by one weak hydrogen bond and several C—H···O interactions (Table 2). Two of the intramolecular C—H···O interactions [involving atoms H(34) and

H(37)] are strong enough to be classified as true hydrogen bonds. The C—H···O interactions involving the H(4) and H(43) atoms represent the most significant intermolecular contacts. Bond lengths, summarized in Table 3, and bond angles are as expected.

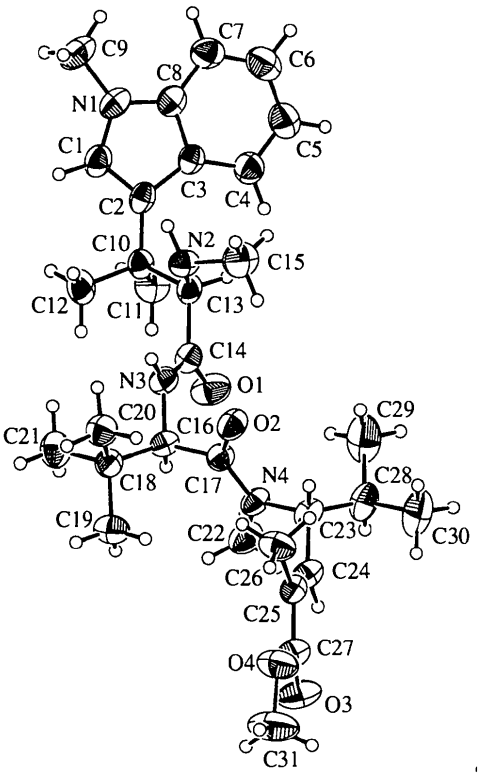


Fig. 1. A perspective view of the title molecule (minor disordered fragment not shown), with 33% probability ellipsoids shown for the non-H atoms. The H atoms shown are those which were refined or are involved in the hydrogen bonds and C—H···O interactions listed in Table 2.

Experimental

The synthesis of the methyl ester of hemiasterlin was carried out by reaction of 5 mg of the isolated hemiasterlin with freshly prepared diazomethane solution (Aldrich MNNG–Diazomethane Kit) in 0.5 ml of CH_3Cl for 1 h at room temperature. The product was recrystallized from a 1:3 acetone/hexane solution to yield clear colorless rod-like crystals.

Crystal data

$C_{31}H_{48}N_4O_4$	Cu $K\alpha$ radiation
M_r = 540.74	λ = 1.5418 Å
Orthorhombic	Cell parameters from 24 reflections
$P2_12_12_1$	θ = 25.5–44.1°
a = 12.2102 (8) Å	μ = 0.589 mm^{-1}
b = 31.464 (2) Å	T = 294 K
c = 8.368 (2) Å	Rod
V = 3214.7 (9) Å^3	0.40 × 0.39 × 0.24 mm
Z = 4	Colorless
D_x = 1.117 Mg m^{-3}	
D_m not measured	

Data collection

Rigaku AFC-6*S* diffractometer	2125 observed reflections [$I > 3\sigma(I)$]
ω–2θ scans	θ_{max} = 77.5°
Absorption correction: azimuthal scans (North, Phillips & Mathews, 1968)	h = −11 → 15
	k = −26 → 39
	l = −10 → 10
T_{min} = 0.865, T_{max} = 1.000	3 standard reflections monitored every 200 reflections
3752 measured reflections	intensity decay: 1.36%
3752 independent reflections	

Refinement

Refinement on F	Extinction correction: Zachariasen (1967) type II, Gaussian isotropic
R = 0.0391	
wR = 0.0375	
S = 2.207	Extinction coefficient: 0.281 (15) × 10^{-5}
2125 reflections	
370 parameters	Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV)
$w = 1/\sigma^2(F_o)$	
$(\Delta/\sigma)_{max}$ = 0.03	
$\Delta\rho_{max}$ = 0.13 e Å^{-3}	
$\Delta\rho_{min}$ = −0.10 e Å^{-3}	

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2)*

$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	U_{eq}
O(1)	0.8394 (3)	0.17722 (9)	0.8203 (4)	0.103 (1)
O(2)	0.6334 (2)	0.25121 (8)	0.5446 (4)	0.0785 (10)
O(3)†	0.8680 (7)	0.4247 (3)	0.383 (1)	0.113 (3)
O(3*)†	0.819 (2)	0.4382 (7)	0.436 (3)	0.115 (8)
O(4)	0.7271 (3)	0.4236 (1)	0.2233 (4)	0.110 (1)
N(1)	0.5499 (3)	−0.00649 (9)	0.8720 (5)	0.079 (1)
N(2)	0.5848 (3)	0.12812 (9)	0.7249 (4)	0.069 (1)
N(3)	0.7413 (3)	0.1744 (1)	0.5932 (5)	0.063 (1)
N(4)	0.7889 (2)	0.28401 (9)	0.6184 (4)	0.066 (1)
C(1)	0.6234 (4)	0.0158 (1)	0.7810 (5)	0.076 (1)
C(2)	0.6614 (3)	0.0501 (1)	0.8616 (5)	0.064 (1)
C(3)	0.6070 (3)	0.0493 (1)	1.0156 (5)	0.062 (1)
C(4)	0.6078 (4)	0.0750 (1)	1.1520 (6)	0.081 (1)
C(5)	0.5424 (4)	0.0649 (2)	1.2785 (6)	0.096 (2)
C(6)	0.4764 (4)	0.0293 (2)	1.2756 (7)	0.101 (2)
C(7)	0.4736 (4)	0.0030 (1)	1.1452 (7)	0.087 (2)
C(8)	0.5384 (4)	0.0134 (1)	1.0163 (6)	0.071 (1)
C(9)	0.4949 (4)	−0.0453 (1)	0.8230 (7)	0.108 (2)
C(10)	0.7435 (3)	0.0822 (1)	0.8019 (5)	0.063 (1)
C(11)	0.8456 (4)	0.0809 (1)	0.9090 (6)	0.088 (2)
C(12)	0.7779 (4)	0.0719 (1)	0.6306 (5)	0.085 (2)
C(13)	0.6899 (3)	0.1274 (1)	0.8092 (5)	0.064 (1)
C(14)	0.7644 (4)	0.1620 (1)	0.7401 (6)	0.067 (1)
C(15)	0.5097 (4)	0.1594 (1)	0.7936 (7)	0.107 (2)
C(16)	0.7948 (3)	0.2100 (1)	0.5154 (5)	0.059 (1)
C(17)	0.7335 (3)	0.2506 (1)	0.5613 (5)	0.063 (1)
C(18)	0.8034 (3)	0.2034 (1)	0.3327 (5)	0.063 (1)
C(19)	0.8655 (3)	0.2410 (1)	0.2602 (5)	0.084 (1)
C(20)	0.6912 (3)	0.1999 (1)	0.2508 (5)	0.078 (1)
C(21)	0.8678 (4)	0.1630 (1)	0.2993 (6)	0.087 (2)
C(22)	0.9073 (3)	0.2839 (1)	0.6525 (6)	0.086 (2)
C(23)	0.7282 (3)	0.3225 (1)	0.6610 (5)	0.068 (1)
C(24)	0.7671 (3)	0.3594 (1)	0.5617 (6)	0.076 (1)

C(25)	0.7202 (3)	0.3752 (1)	0.4327 (5)	0.065 (1)
C(26)	0.6164 (4)	0.3587 (1)	0.3629 (6)	0.091 (2)
C(27)	0.7772 (4)	0.4109 (1)	0.3530 (7)	0.081 (2)
C(28)	0.7314 (4)	0.3321 (1)	0.8404 (6)	0.087 (2)
C(29)	0.6898 (5)	0.2943 (2)	0.9352 (6)	0.132 (2)
C(30)	0.6637 (5)	0.3716 (2)	0.8754 (6)	0.125 (2)
C(31)	0.7805 (5)	0.4570 (2)	0.1330 (8)	0.154 (3)

† Partial occupancy (see below).

Table 2. *Geometry of hydrogen bonds and C—H···O interactions (Å, °)*

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C(6)—H(4)···O(3*^{i})	0.98	2.46	3.25 (3)	138
C(11)—H(11)···O(1)	0.98	2.51	3.122 (5)	120
N(3)—H(20)···N(2)	0.76 (4)	2.28 (4)	2.644 (5)	110 (4)
C(16)—H(21)···O(1)	0.98	2.48	2.805 (5)	99
C(20)—H(26)···O(2)	0.98	2.42	3.025 (5)	120
C(23)—H(34)···O(2)	0.98	2.22	2.706 (4)	109
C(24)—H(35)···O(3)	0.98	2.45	2.82 (1)	102
C(24)—H(35)···O(3*)	0.98	2.45	2.77 (3)	98
C(26)—H(37)···O(4)	0.98	2.22	2.713 (5)	109
C(30)—H(43)···O(4^{ii})	0.98	2.52	3.427 (6)	154

Symmetry codes: (i) $x-\frac{1}{2}, \frac{1}{2}-y, 2-z$; (ii) $x, y, 1+z$.

Table 3. *Summary of bond lengths (Å)*

Bond type	Range	Mean
C—$C_{aromatic}$	1.364 (6)–1.405 (5)	1.383 (7)
C=C	1.318 (5)–1.355 (5)	1.337 (7)
C—$C_{aliphatic}$	1.516(7)–1.568 (5)	1.534 (6)
C_{sp^2}—C_{sp^2}	1.450 (6)–1.481 (6)	1.466 (8)
C_{sp^3}—C_{sp^2}	1.489 (5)–1.532 (5)	1.513 (6)
N—C_{sp^2}	1.367 (5)–1.369 (5)	1.368 (7)
N—C_{sp^3}	1.449 (5)–1.474 (4)	1.461 (5)
O=C	1.22 (1)–1.232 (5)	1.23 (1)
O—$C_{carboxylate}$	1.307 (5)	
O—C_{ester}	1.452 (6)	

The structure was solved by direct methods using *SIR*92 (Altomare *et al.*, 1994) and expanded using Fourier techniques (Beurskens *et al.*, 1994). All calculations were performed using *TEXSAN* (Molecular Structure Corporation, 1992) and *MSC/AFC Diffractometer Control Software* (Molecular Structure Corporation, 1988) was used for data collection and cell refinement. The amine H atoms were refined with isotropic displacement parameters. The remaining H atoms were fixed in calculated positions (methyl groups staggered, with C—H 0.98 Å and displacement parameters 20% larger than those of the parent atoms). The partial disorder of the crystal structure involves the carbonyl O(3) atom of the ester fragment. The occupancies of the two positions were adjusted as the refinement progressed to yield approximately equal displacement parameters, the final values being 0.71 and 0.29 for O(3) and O(3*), respectively. The absolute configuration was based on the known chiralities of two centers. A parallel refinement of the opposite enantiomer gave slightly higher residuals (R = 0.0392 and wR = 0.0376).

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry, including torsion angles and contact distances, have been deposited with the IUCr (Reference: FG1120). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

References

Altomare, A., Cascarano, G., Giacovazzo, C., Guagliardi, A., Burla, M. C., Polidori, G. & Camalli, M. (1994). *J. Appl. Cryst.* **27**, 435.

Beurskens, P. T., Admiraal, G., Beurskens, G., Bosman, W. P., de Gelder, R., Israël, R. & Smits, J. M. M. (1994). *The DIRDIF Program System.* Technical Report. Crystallography Laboratory, University of Nijmegen, The Netherlands.

Coleman, J. E., de Silva, E. D., Kong, F., Andersen, R. J. & Allen, T. M. (1995). *Tetrahedron*, **39**, 10653–10662.

Crews, P., Farias, J. J., Emrich, R. & Keifer, P. A. (1994). *J. Org. Chem.* **59**, 2932–2934

Fusetani, N. & Matsunaga, S. (1993). *Chem. Rev.* **93**, 1793–1806

Molecular Structure Corporation (1988). *MSC/AFC Diffractometer Control Software.* MSC, 3200 Research Forest Drive, The Woodlands, TX 77381, USA.

Molecular Structure Corporation (1992). *TEXSAN. Single Crystal Structure Analysis Software.* MSC, 3200 Research Forest Drive, The Woodlands, TX 77381, USA.

North, A. C. T., Phillips, D. C. & Mathews, F. S. (1968). *Acta Cryst.* A**24**, 351–359.

Roberge, M., Anderson, H., Coleman, J. E. & Andersen, R. J. (1995). Unpublished results.

Talpir, R., Benayahu, Y., Kashman, Y., Pannell, L. & Schleyer, M. (1994). *Tetrahedron Lett.* **35**, 4453–4456.

Zachariasen, W. H. (1967). *Acta Cryst.* **23**, 558–564.

Acta Cryst. (1996). C**52**, 1527–1529

Humilinolide D

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Abstract

The title molecule, methyl α,10-bis(acetoxy)-4-(3-furanyl)-1,4,4a,5,6,6a,7,8,9,10,11,12b-dodecahydro-11-hydroxy-4a,7,9,9-tetramethyl-2,13-dioxo-7,11-methano-2*H*-cyclooctа[*f*][2]benzopyran-8-acetate, $C_{31}H_{38}O_{11}$, consists of four six-membered rings (*A*, *B*, *C* and *D*) and a five-membered furan ring (*E*). The *A* ring is fused at C(2)—C(1)—C(10) to the *B* ring. The *B*/*C* and *C*/*D* rings are *trans*- and *cis*-fused, respectively. Rings *A*, *B*, *C* and *D* adopt conformations intermediate between twist $^2T_4$ and boat $B_{4,1}$, intermediate between half-chair $^1H_6$ and envelope ^1E, distorted chair $^1C_4$ and half-chair

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