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Di- and tripeptide segments of zervamicin II-2: Z-Thr(OBn)-Aib-N(Me)Ph and Z-Val-Aib-Hyp(OBn)-OMe

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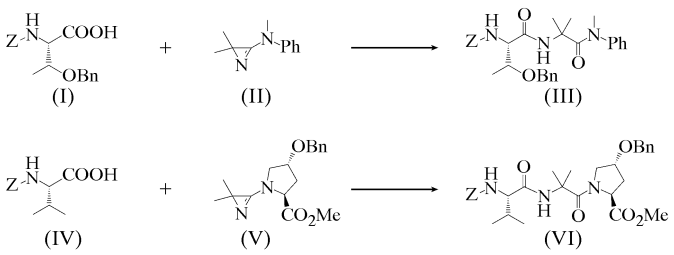
The title compounds, *O*-benzyl-*N*-(benzyloxycarbonyl)threonyl-2,*N*-dimethylalaninanilide, $C_{30}H_{35}N_3O_5$, and methyl (4*R*)-4-benzyloxy-*N*-(benzyloxycarbonyl)valyl-2-(methylalanyl)prolinate, $C_{30}H_{39}N_3O_7$, were obtained from the 'azirine coupling' of the corresponding protected amino acids with 2,2,*N*-trimethyl-2*H*-azirin-3-amine and methyl (4*R*)-4-(benzyloxy)-*N*-(2,2-dimethyl-2*H*-azirin-2-yl)prolinate, respectively. The Aib unit in each molecule has the greatest turn- or helix-inducing effect on the molecular conformation. Intermolecular N—H···O interactions link the molecules of the tripeptide into sheets and those of the dipeptide into extended chains.

Comment

In recent years, 2*H*-azirin-3-amines have been shown to be useful synthons for 2,2-disubstituted glycines, such as 2-aminoisobutyric acid (Aib, 2-methylalanine), in peptide synthesis (Wipf & Heimgartner, 1990; Heimgartner, 1991). Furthermore, methyl (2*H*-azirin-3-yl)prolinates have proved to be convenient dipeptide synthons (Luykx *et al.*, 1996; Breitenmoser *et al.*, 2001). This novel method, the 'azirine/oxazolone method', for the introduction of sterically hindered α,α-disubstituted α-amino acids into peptides, is especially suitable for the preparation of peptaibols, which are amphiphilic membrane-active peptide antibiotics (Benedetti *et al.*, 1982) containing up to 50% of the non-protein amino acid Aib. These metabolites of some fungi have antibacterial properties because of their ability to self-associate in lipid membranes to form ion channels (Latorre & Alvarez, 1981; Chugh *et al.*, 2002; Duclohier *et al.*, 2003). A condition for this ability is a helical conformation of the molecule, which is induced and stabilized by the presence of Aib (Karle *et al.*, 1989; Toniolo *et al.*, 1993; Di Blasio *et al.*, 1993). The helical structure of some peptaibols has been established by X-ray crystallography; for example, for zervamicin IIB (Karle *et al.*, 1991, 1994; Karle, 1996) and antiamoebin (Karle *et al.*, 1998). The data for more than 300 peptaibols or segments of peptaibols, including crystal structures, are now available from the online peptaibol database maintained by Chugh and Wallace in London (Whitmore & Wallace, 2004; URL: http://www.cryst.bbk.ac.uk/peptaibol).



Z = $PhCH_2OCO-$ and Bn = $PhCH_2-$

Recently, the 'azirine/oxazolone method' has been used for the synthesis of peptaibols or segments thereof, for example, alamethicin F30 (Wipf & Heimgartner, 1990), trichotoxin A-50(G) (Altherr & Heimgartner, 1991; Altherr, 1994), antiamoebin (Altherr & Heimgartner, 1993), tichovirin I 1B (Luykx *et al.*, 1996, 2003), hypomurocin A1 (Pradeille *et al.*, 2005) and zervamicin II-2 (Pradeille & Heimgartner, 2003). In the last-mentioned paper, the 6-16 segment was prepared by the coupling of the segments 6-7, 8-10 and 11-16, which had been obtained by the reaction of the corresponding amino acids with 2*H*-azirin-3-amines. Treatment of the threonine derivative, (I), with the Aib synthon, (II), yielded the title dipeptide, (III), and the analogous reaction of the N-protected valine, (IV), with the Aib–Hyp dipeptide synthon, (V), led to the title tripeptide, (VI) (see scheme above). The X-ray crystallographic analyses of compounds (III) and (VI) were undertaken in order to elucidate their molecular structures and conformations and to investigate their hydrogen-bonding interactions, and the results are presented here.

The molecular structures of compounds (III) and (VI) are shown in Figs. 1 and 2, respectively. The bond lengths and

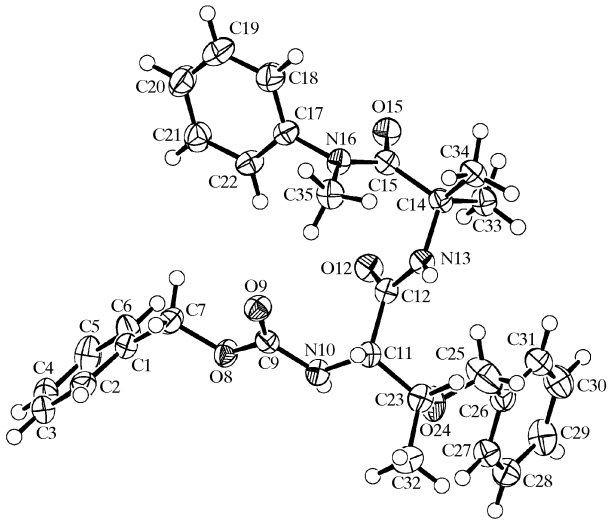


Figure 1
A view of the molecule of (III), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are represented by circles of arbitrary size.

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angles fall within normal ranges. The torsion angles along the peptide backbones of (III) and (VI) are listed in Table 1, together with those of the related compound, Z-Val-Aib-Pro-OH (Val is valine and Pro is proline; Pradeille *et al.*, 2005). Although there are small variations in the magnitudes of the torsion angles, their signs are consistent and on the whole the values are quite similar. The two consecutive small torsion angles on either side of atom C14 in the Aib group confirm the turn- or helix-inducing property of Aib in a peptide chain. The turns occur despite the absence of any significant intramolecular hydrogen bonds. The proline ring in compound (VI) has a slightly distorted half-chair conformation twisted on C26—C27, with a value for the φ_2 puckering parameter (Cremer & Pople, 1975) of 94.9 (4)° for the atom sequence N16—C17—C27—C26—C25. Atoms C26 and C27 lie 0.367 (2) and −0.206 (2) Å, respectively, from the plane defined by atoms N16, C17 and C25.

In the structure of compound (III), the amide H atom of Aib forms an intermolecular hydrogen bond with the carbonyl O atom of Aib of a neighbouring molecule (Table 2). This thereby links the molecules into extended chains which run parallel to the [010] direction (Fig. 3) and can be described by a graph-set motif (Bernstein *et al.*, 1995) of $C(5)$. The amide H atom of tyrosine (Tyr) is not involved in any intermolecular interactions. Although this H atom is 2.50 (2) Å from the O atom of the benzoyl substituent on Thr, this intramolecular interaction is probably insignificant, given the very sharp N—H···O angle of 104 (2)°.

In the structure of compound (VI), the amide H atom of Val forms an intermolecular hydrogen bond with the C-terminal carbonyl O atom of a neighbouring molecule (Table 3). This interaction links the molecules into extended chains which run parallel to the [010] direction and can be described by a graph-

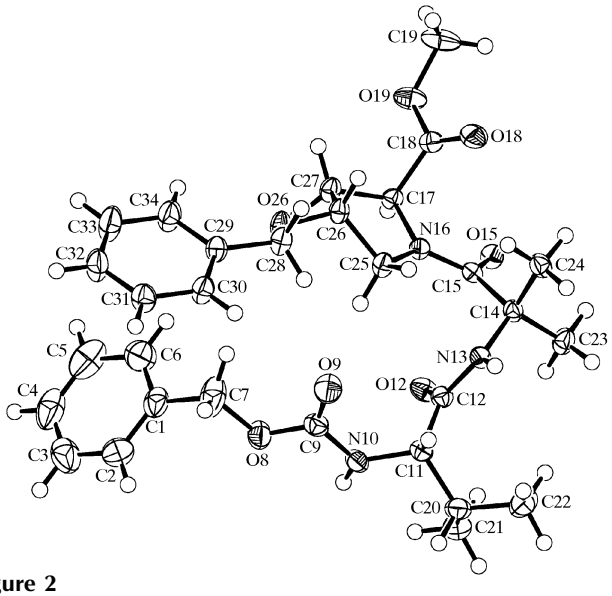

Figure 2
A view of the molecule of (VI), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are represented by circles of arbitrary size.

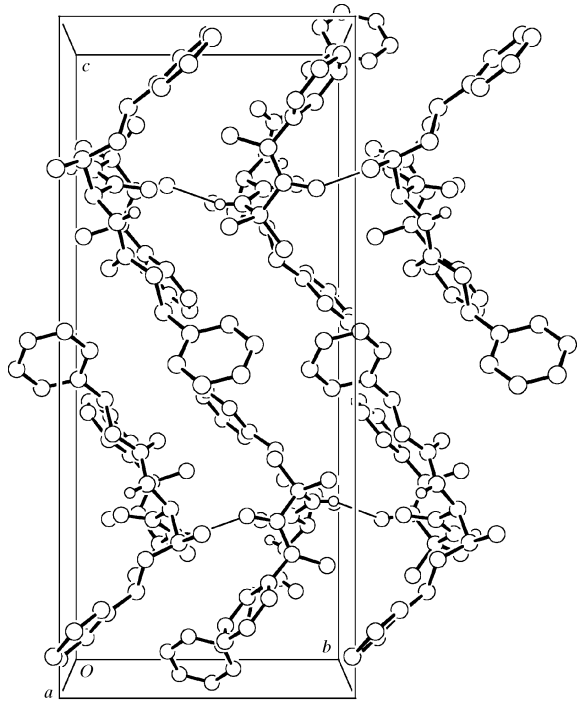

Figure 3
The crystal packing in (III), viewed along the *a* axis and showing the hydrogen-bonded chains. Most of the H atoms have been omitted for clarity. Hydrogen bonds are represented by thin lines.

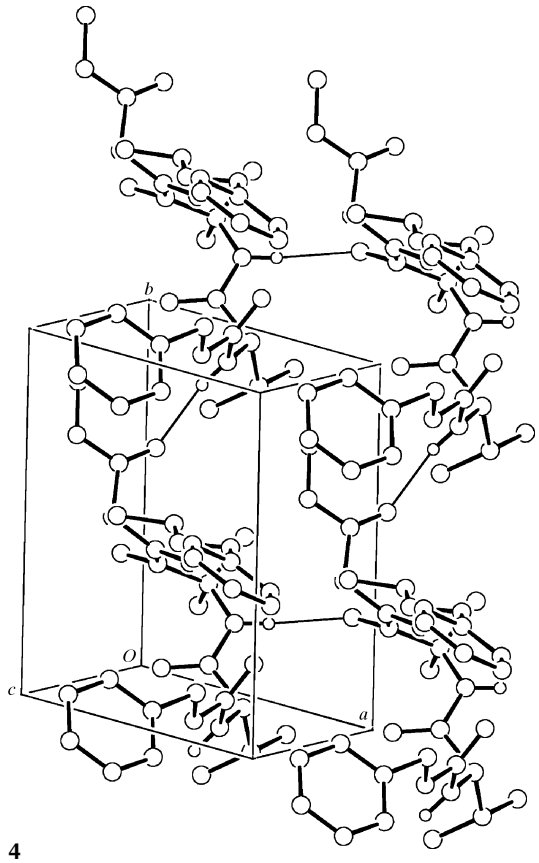

Figure 4
The crystal packing in (VI), showing a hydrogen-bonded sheet with the $R_4^4(28)$ motif. Most of the H atoms have been omitted for clarity. Hydrogen bonds are represented by thin lines.

set motif of $C(11)$. As with compound (III), the amide H atom of Aib forms an intermolecular hydrogen bond with the carbonyl O atom of Aib of a different neighbouring molecule. This interaction links the molecules into extended chains which run parallel to the [100] direction and can be described by a graph-set motif of $C(5)$. The combination of the hydrogen-bonding interactions links the molecules into two-dimensional networks which lie parallel to the (001) plane (Fig. 4). Within these networks, the two different hydrogen-bonding interactions unite to form a ring which can be described by the binary graph-set motif of $R_4^4(28)$.

Experimental

The syntheses of compounds (III) and (VI) have already been described by Pradeille & Heimgartner (2003). Suitable crystals were obtained by slow evaporation of solutions of the compounds in deuterochloroform and methanol–hexane–ethyl acetate, respectively, at room temperature [m.p. 407–408 K for (III) and 403–407 K for (VI)].

Compound (III)

Crystal data

$C_{30}H_{35}N_3O_5$
M_r = 517.62
Orthorhombic, $P2_12_12_1$
a = 10.4178 (2) Å
b = 10.6996 (2) Å
c = 24.6636 (5) Å
V = 2749.16 (9) Å^3
Z = 4
D_x = 1.251 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 2773 reflections
θ = 2.0–25.0°
μ = 0.09 mm^{-1}
T = 160 (1) K
Tablet, colourless
0.22 × 0.10 × 0.05 mm

Data collection

Nonius KappaCCD area-detector diffractometer
φ and ω scans with κ offsets
30620 measured reflections
2759 independent reflections
2388 reflections with $I > 2\sigma(I)$
R_{int} = 0.058
θ_{max} = 25.0°
$h = 0 \rightarrow 12$
$k = 0 \rightarrow 12$
$l = 0 \rightarrow 29$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.037
$wR(F^2)$ = 0.090
S = 1.07
2757 reflections
356 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0473P)^2 + 0.3586P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.17 e Å^{-3}
$\Delta\rho_{min}$ = −0.15 e Å^{-3}
Extinction correction: *SHELXL97* (Sheldrick, 1997)
Extinction coefficient: 0.0090 (13)

Table 1
A comparison of selected peptide backbone torsion angles (°).

	(III)	(VI)	*Z*-Val-Aib-Pro-OH[a]
O8—C9—N10—C11	167.11 (19)	170.08 (18)	178.4 (4)
C9—N10—C11—C12	−62.6 (3)	−78.8 (2)	−89.7 (5)
N10—C11—C12—N13	162.4 (2)	137.62 (18)	164.4 (4)
C11—C12—N13—C14	179.82 (19)	167.92 (17)	177.2 (4)
C12—N13—C14—C15	50.0 (3)	50.5 (2)	52.3 (6)
N13—C14—C15—N16	51.6 (3)	47.0 (2)	35.8 (6)
C14—C15—N16—C17	−170.7 (2)	161.98 (17)	172.7 (4)
C15—N16—C17—C18	−103.3 (3)	−69.2 (2)	−78.5 (5)
N16—C17—C18—O19		173.53 (16)	172.3 (4)

Note: (*a*) Pradeille *et al.* (2005).

Table 2
Hydrogen-bond geometry (Å, °) for (III).

D—H···A	D—H	H···A	D···A	D—H···A
N10—H10···O24	0.84 (3)	2.50 (2)	2.823 (3)	104 (2)
N13—H13···O15^{i}	0.82 (2)	2.35 (3)	3.088 (3)	149 (2)

Symmetry code: (i) $-x+2, y-\frac{1}{2}, -z+\frac{3}{2}$.

Compound (VI)

Crystal data

$C_{30}H_{39}N_3O_7$
M_r = 553.65
Triclinic, $P\overline{1}$
a = 6.2705 (1) Å
b = 9.7577 (2) Å
c = 13.2491 (3) Å
α = 106.6479 (13)°
β = 94.2733 (10)°
γ = 105.7257 (12)°
V = 737.36 (3) Å^3
Z = 1
D_x = 1.247 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 3287 reflections
θ = 2.0–27.5°
μ = 0.09 mm^{-1}
T = 160 (1) K
Prism, colourless
0.33 × 0.25 × 0.15 mm

Data collection

Nonius KappaCCD area-detector diffractometer
φ and ω scans with κ offsets
17488 measured reflections
3359 independent reflections
3096 reflections with $I > 2\sigma(I)$
R_{int} = 0.041
θ_{max} = 27.5°
$h = 0 \rightarrow 8$
$k = -12 \rightarrow 12$
$l = -17 \rightarrow 16$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.036
$wR(F^2)$ = 0.085
S = 1.07
3359 reflections
375 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0367P)^2 + 0.1302P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.15 e Å^{-3}
$\Delta\rho_{min}$ = −0.16 e Å^{-3}
Extinction correction: *SHELXL97* (Sheldrick, 1997)
Extinction coefficient: 0.090 (9)

Table 3
Hydrogen-bond geometry (Å, °) for VI.

D—H···A	D—H	H···A	D···A	D—H···A
N10—H10···O18^{i}	0.90 (3)	2.06 (3)	2.927 (3)	163 (2)
N13—H13···O15^{ii}	0.89 (2)	2.17 (3)	3.060 (2)	175 (2)

Symmetry codes: (i) $x, y-1, z$; (ii) $x+1, y, z$.

The amide H atoms were located in difference Fourier maps and their positions were refined freely along with individual isotropic displacement parameters. The methyl H atoms were constrained to an ideal geometry (C—H = 0.98 Å), with $U_{iso}(H) = 1.5U_{eq}(C)$, but were allowed to rotate freely about the C—C bonds. All other H atoms were placed in geometrically idealized positions and constrained to ride on their parent C atoms at distances of 0.95, 0.99 and 1.00 Å for phenyl, methylene and methine groups, respectively, and with $U_{iso}(H) = 1.2U_{eq}(C)$. As there are no significant anomalous dispersion effects with these compounds, Friedel opposites were merged prior to the final cycles of refinement. The enantiomers used in the refinement models were chosen so as to correspond with the chirality of the stereogenic centres known from the syntheses of the compounds. For (III), two low-angle reflections were omitted from the final cycles of refinement because their observed intensities were

much lower than the calculated values, as a result of being partially obscured by the beam stop.

For both compounds, data collection: *COLLECT* (Nonius, 2000); cell refinement: *DENZO* (Otwinowski & Minor, 1997); data reduction: *DENZO* and *SCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEPII* (Johnson, 1976); software used to prepare material for publication: *SHELXL97* and *PLATON* (Spek, 2003).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: TR3003). Services for accessing these data are described at the back of the journal.

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