# Crystal structure of *cyclo*(2-hydroxy-*i*-valeryl-isoleucyl-2-hydroxy-*i*-valeryl-alanyl-threonyl) dihydrate, $C_{23}H_{39}N_3O_8 \cdot 2H_2O$

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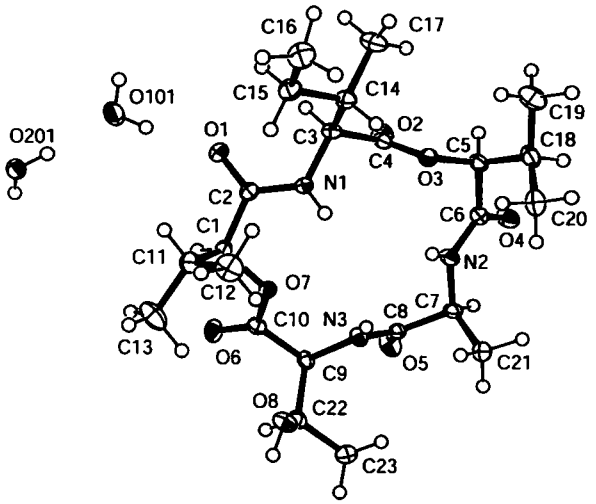


**Abstract**

$C_{23}H_{43}N_3O_{10}$, monoclinic, $P12_11$ (no. 4), $a = 7.914(1)$ Å, $b = 16.509(3)$ Å, $c = 10.522(2)$ Å, $\beta = 92.484(1)°$, $V = 1373.4$ Å$^3$, $Z = 2$, $R_{gt}(F) = 0.025$, $wR_{ref}(F) = 0.028$, $T = 150$ K.

**Source of material**

The strain *Trichothecium roseum* ATCC 36473 (isolated from an apple) was cultivated by submerged cultivation in 10 l fermentor on Czapek Dox medium 7 days at 24 °C. The fermentation broth was filtered and roseotoxins were extracted from medium by dichloromethane. Crude roseotoxins were purified by column chromatography on a silica gel (Merck 60, a stepwise gradient 1-10 % methanol in dichloromethane) and by a novel type of preparative NP-HPLC on an amino modified column (Watrex Biosphere SI N, 5 $\mu$m, 250 × 12 mm, I.D., isocratic elution with isopropanol/*n*-hexane, 1:4 *v/v*, 5 ml/min, detector set at 235 nm). The fraction containing the mixture of roseotoxins A and Z (about 2:3 *w/w*) was crystallized from dichloromethane/methanol providing directly a single crystal of roseotoxin Z. Roseotoxins were further characterized by positive-ion electrospray (ESI) mass spectra acquired on Finnigan LCQ-DECA quadrupole ion trap mass spectrometer (Finnigan MAT, San Jose, CA, USA) [1].

**Discussion**

Cyclopentapeptides are studied as interesting conformational templates in the rational design of new pharmaceuticals [2]. About ten structures of conformationally restricted proline-containing cyclic peptides can be found in the CCDC, however, structures of a cyclic pentapeptide with alifatic amino acids or a cyclic pentadepsipeptide are apparently entirely missing.

*Trichothecium roseum* has been described as a producer of several cyclic hexadepsipeptides [1]. The title structure is related to the cyclic pentadepsipeptide roseotoxin S [3], but exhibits different sequence of building units indicating thus the possibility that the original structure assignment of roseotoxin S need not be correct. Since the original material was not available to us for comparison, the new compound is denominated as roseotoxin Z. Roseotoxin Z provided a molecular ion *m/z* 486 $[M+H]^+$ corresponding to the composition $C_{23}H_{40}N_{30}O_8^+$. The CID mass spectrum of ion $[M+H]^+$ provided consecutive elimination of carbon monoxide and water *m/z* 458 $[MH-CO]^+$, 440 $[MH-CO-H_2O]^+$, and one dominating ring splitting being represented by fragment ion series 385 ($b_4$), 357 ($a_4$), 314 ($b_3$), and 214 ($b_2$). This ion series is in agreement with sequences either *cyclo*(Ile–HiV–HiV–Ala–Thr) or *cyclo*(HiV–Ile–HiV–Ala–Thr), where HiV stands for 2-hydroxy-isovaleric acid. The latter structure was confirmed by crystal structure determination providing in addition an assignment of its all *trans* (*S*,*S*,*S*,*S*,*S*)-configuration. All constituents possess negative $\Phi$ and $\Psi$ values ($\Phi^1 = -131.2(1)$, $\Phi^2 = -128.5(2)$, $\Phi^3 = -81.1(2)$, $\Phi^4 = -126.8(2)$, $\Phi^5 = -128.8(2)$, $\Psi^1 = -25.8(2)$, $\Psi^2 = -85.0(2)$, $\Psi^3 = -24.2(2)$, $\Psi^4 = -58.6(2)$, $\Psi^5 = -19.8(2)$).

In spite of the peptide backbone conformation together with the lack of intramolecular H bonds does not correspond to usual predefined structural types, the structure can be tentatively assigned as "closely resembling $\beta$I-turn". The presence of two (*S*)-L-HiV residues is very unusual since apparently only (*R*)-D-HiV was so far encountered in various depsipeptides, e.g., in beauvericin [4], enniatins [5], or valinomycin [6]. Most marked feature of the structure is its bi-polar arrangement with all C=O groups oriented to one site of the ring structure and both aliphatic chains and all three NH groups oriented out off the opposite site. Surprisingly, any intramolecular H bond is absent, but there are nine intermolecular H bonds in the structure. The water oxygen O201 plays the key role in the H bond system, since it is involved in overall five hydrogen bonds. Three of them point to all roseotoxin N–H groups, one links the second water molecule, and one is bonded for O5 of a symmetry related roseotoxin Z molecule. The O101 water oxygen forms three hydrogen bonds: with water O201 and two carbonyl oxygens O8 and O1 of symmetry related roseotoxin Z molecule. In addition to water based hydrogen bonds, threonine OH group forms H bond with O4 from symmetry related roseotoxin Z molecule.

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**Table 1.** Data collection and handling.

| | |
|---|---|
| Crystal: | colorless plate, size 0.50 × 0.47 × 0.15 mm |
| Wavelength: | Mo $K_\alpha$ radiation (0.71073 Å) |
| $\mu$: | 0.98 $cm^{-1}$ |
| Diffractometer, scan mode: | Nonius KappaCCD, $\omega/2\theta$ |
| $2\theta_{max}$: | 54.96° |
| $N(hkl)_{measured}$, $N(hkl)_{unique}$: | 6296, 3264 |
| Criterion for $I_{obs}$, $N(hkl)_{gt}$: | $I_{obs} > 3\ \sigma(I_{obs})$, 2942 |
| $N(param)_{refined}$: | 497 |
| Programs: | SIR92 [7], CRYSTALS [8] |

**Table 2.** Atomic coordinates and displacement parameters (in Å$^2$).

| Atom | Site | $x$ | $y$ | $z$ | $U_{iso}$ |
|---|---|---|---|---|---|
| H(1) | 2a | 0.452(3) | 0.123(2) | 0.807(2) | 0.026(6) |
| H(2) | 2a | 0.314(3) | −0.021(2) | 0.689(2) | 0.035(6) |
| H(3) | 2a | 0.194(3) | −0.005(2) | 0.893(2) | 0.040(6) |
| H(8) | 2a | 0.147(3) | −0.018(2) | 1.257(3) | 0.043(7) |
| H(11) | 2a | 0.250(3) | 0.257(1) | 0.996(2) | 0.020(5) |
| H(31) | 2a | 0.494(2) | 0.245(1) | 0.635(2) | 0.013(4) |
| H(51) | 2a | 0.365(3) | 0.040(1) | 0.387(2) | 0.023(5) |
| H(71) | 2a | 0.001(2) | −0.089(1) | 0.627(2) | 0.018(5) |
| H(91) | 2a | −0.099(3) | 0.065(1) | 0.958(2) | 0.016(5) |
| H(111) | 2a | 0.525(3) | 0.272(2) | 1.085(2) | 0.034(6) |
| H(121) | 2a | 0.690(3) | 0.165(2) | 1.164(3) | 0.045(7) |
| H(122) | 2a | 0.546(4) | 0.102(2) | 1.097(3) | 0.051(8) |
| H(123) | 2a | 0.663(3) | 0.155(2) | 1.010(3) | 0.049(8) |
| H(131) | 2a | 0.472(3) | 0.224(2) | 1.296(2) | 0.038(6) |

**Table 2.** Continued.

| Atom | Site | $x$ | $y$ | $z$ | $U_{iso}$ |
|---|---|---|---|---|---|
| H(132) | 2a | 0.302(4) | 0.261(2) | 1.224(3) | 0.054(8) |
| H(133) | 2a | 0.320(4) | 0.163(2) | 1.232(3) | 0.062(9) |
| H(141) | 2a | 0.739(3) | 0.115(1) | 0.664(2) | 0.020(5) |
| H(151) | 2a | 0.781(3) | 0.216(2) | 0.833(2) | 0.028(5) |
| H(152) | 2a | 0.781(3) | 0.287(2) | 0.722(2) | 0.039(7) |
| H(161) | 2a | 1.062(3) | 0.248(2) | 0.811(3) | 0.045(7) |
| H(162) | 2a | 1.043(4) | 0.160(2) | 0.742(3) | 0.059(9) |
| H(163) | 2a | 1.044(3) | 0.241(2) | 0.652(3) | 0.048(7) |
| H(171) | 2a | 0.877(3) | 0.181(2) | 0.496(2) | 0.042(7) |
| H(172) | 2a | 0.745(3) | 0.254(2) | 0.493(3) | 0.046(7) |
| H(173) | 2a | 0.688(3) | 0.164(2) | 0.446(2) | 0.042(7) |
| H(181) | 2a | 0.462(3) | −0.094(1) | 0.365(2) | 0.022(5) |
| H(191) | 2a | 0.754(4) | −0.069(2) | 0.338(3) | 0.059(8) |
| H(192) | 2a | 0.738(3) | 0.008(2) | 0.432(3) | 0.049(7) |
| H(193) | 2a | 0.634(4) | 0.010(2) | 0.293(3) | 0.061(9) |
| H(201) | 2a | 0.654(4) | −0.155(2) | 0.511(3) | 0.045(7) |
| H(202) | 2a | 0.639(3) | −0.084(2) | 0.611(2) | 0.034(6) |
| H(203) | 2a | 0.475(3) | −0.142(2) | 0.578(2) | 0.035(6) |
| H(211) | 2a | 0.057(4) | −0.183(2) | 0.801(3) | 0.049(8) |
| H(212) | 2a | 0.240(3) | −0.142(2) | 0.830(2) | 0.038(6) |
| H(213) | 2a | 0.192(3) | −0.194(2) | 0.694(3) | 0.044(7) |
| H(221) | 2a | −0.079(3) | 0.038(1) | 1.162(2) | 0.022(5) |
| H(231) | 2a | −0.196(4) | −0.073(2) | 1.049(3) | 0.064(9) |
| H(232) | 2a | −0.096(3) | −0.106(2) | 1.173(3) | 0.038(6) |
| H(233) | 2a | −0.005(3) | −0.114(2) | 1.039(2) | 0.038(7) |
| H(1011) | 2a | 0.524(4) | 0.398(2) | 0.911(3) | 0.07(1) |
| H(1012) | 2a | 0.658(4) | 0.453(2) | 0.899(3) | 0.046(7) |
| H(2011) | 2a | 0.406(4) | 0.497(2) | 1.188(3) | 0.050(7) |
| H(2012) | 2a | 0.515(4) | 0.481(2) | 1.098(3) | 0.047(8) |

**Table 3.** Atomic coordinates and displacement parameters (in Å$^2$).

| Atom | Site | $x$ | $y$ | $z$ | $U_{11}$ | $U_{22}$ | $U_{33}$ | $U_{12}$ | $U_{13}$ | $U_{23}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| O(1) | 2a | 0.4349(2) | 0.30587(8) | 0.8286(1) | 0.0326(7) | 0.0163(6) | 0.0266(6) | −0.0023(5) | 0.0060(5) | 0.0000(5) |
| O(2) | 2a | 0.2921(2) | 0.1575(1) | 0.5049(1) | 0.0262(6) | 0.0357(8) | 0.0267(6) | 0.0062(5) | −0.0057(5) | −0.0031(5) |
| O(3) | 2a | 0.4789(2) | 0.05892(9) | 0.5575(1) | 0.0198(5) | 0.0205(6) | 0.0178(5) | −0.0031(4) | −0.0001(4) | −0.0008(5) |
| O(4) | 2a | 0.1253(2) | −0.0547(1) | 0.4331(1) | 0.0244(6) | 0.0394(8) | 0.0166(5) | −0.0090(5) | −0.0018(4) | −0.0017(5) |
| O(5) | 2a | −0.1586(2) | −0.0142(1) | 0.7806(1) | 0.0156(5) | 0.0451(8) | 0.0299(6) | 0.0023(5) | −0.0032(5) | −0.0088(6) |
| O(6) | 2a | 0.0286(2) | 0.18602(9) | 1.0708(1) | 0.0245(6) | 0.0246(6) | 0.0378(7) | −0.0008(5) | 0.0120(5) | −0.0104(6) |
| O(7) | 2a | 0.2577(1) | 0.13590(8) | 0.9765(1) | 0.0145(5) | 0.0161(5) | 0.0204(5) | −0.0019(4) | 0.0031(4) | −0.0007(4) |
| O(8) | 2a | 0.1554(2) | −0.0009(1) | 1.1805(1) | 0.0239(6) | 0.0363(7) | 0.0180(5) | 0.0009(6) | 0.0013(4) | 0.0037(6) |
| O(101) | 2a | 0.5791(2) | 0.4371(1) | 0.9465(2) | 0.059(1) | 0.054(1) | 0.0374(8) | −0.0326(9) | 0.0253(8) | −0.0250(8) |
| O(201) | 2a | 0.5062(2) | 0.50070(9) | 1.1685(1) | 0.0198(6) | 0.0263(6) | 0.0217(6) | −0.0032(5) | 0.0015(4) | −0.0031(5) |
| N(1) | 2a | 0.4583(2) | 0.1725(1) | 0.7828(1) | 0.0207(6) | 0.0156(7) | 0.0173(6) | −0.0011(5) | 0.0030(5) | 0.0019(5) |
| N(2) | 2a | 0.2221(2) | −0.0348(1) | 0.6383(1) | 0.0171(6) | 0.0253(7) | 0.0150(6) | −0.0033(5) | 0.0021(5) | −0.0002(5) |
| N(3) | 2a | 0.0894(2) | 0.0048(1) | 0.8906(1) | 0.0131(6) | 0.0229(7) | 0.0181(6) | 0.0006(5) | 0.0026(5) | −0.0031(6) |
| C(1) | 2a | 0.3387(2) | 0.2153(1) | 0.9841(2) | 0.0183(7) | 0.0158(7) | 0.0202(7) | −0.0012(6) | 0.0018(6) | −0.0018(6) |
| C(2) | 2a | 0.4147(2) | 0.2341(1) | 0.8571(2) | 0.0156(7) | 0.0172(7) | 0.0205(7) | −0.0011(6) | −0.0008(5) | 0.0006(6) |
| C(3) | 2a | 0.5218(2) | 0.1875(1) | 0.6563(2) | 0.0194(7) | 0.0195(8) | 0.0166(7) | −0.0014(6) | 0.0020(6) | 0.0036(6) |
| C(4) | 2a | 0.4165(2) | 0.1349(1) | 0.5636(1) | 0.0196(7) | 0.0242(8) | 0.0152(7) | −0.0018(6) | 0.0043(6) | 0.0009(6) |
| C(5) | 2a | 0.3957(2) | 0.0064(1) | 0.4637(1) | 0.0213(7) | 0.0251(8) | 0.0132(6) | −0.0038(7) | 0.0019(5) | −0.0015(6) |
| C(6) | 2a | 0.2336(2) | −0.0295(1) | 0.5118(2) | 0.0205(7) | 0.0210(8) | 0.0175(7) | 0.0010(6) | 0.0021(6) | −0.0012(6) |
| C(7) | 2a | 0.0841(2) | −0.0780(1) | 0.6968(2) | 0.0211(8) | 0.0226(8) | 0.0179(7) | −0.0062(6) | 0.0041(6) | −0.0013(6) |
| C(8) | 2a | −0.0055(2) | −0.0252(1) | 0.7923(2) | 0.0183(7) | 0.0180(7) | 0.0165(7) | −0.0034(6) | 0.0027(5) | 0.0007(6) |
| C(9) | 2a | 0.0131(2) | 0.0514(1) | 0.9906(2) | 0.0141(7) | 0.0217(8) | 0.0180(7) | −0.0003(6) | 0.0035(5) | −0.0037(6) |
| C(10) | 2a | 0.0989(2) | 0.1320(1) | 1.0178(2) | 0.0170(7) | 0.0209(8) | 0.0181(7) | 0.0007(6) | 0.0031(5) | 0.0005(6) |
| C(11) | 2a | 0.4696(2) | 0.2200(1) | 1.0954(2) | 0.0255(8) | 0.0256(9) | 0.0210(8) | −0.0050(7) | −0.0019(6) | −0.0017(7) |
| C(12) | 2a | 0.6012(3) | 0.1529(2) | 1.0908(2) | 0.0275(9) | 0.043(1) | 0.031(1) | 0.0030(9) | −0.0072(8) | 0.0027(9) |
| C(13) | 2a | 0.3832(3) | 0.2196(2) | 1.2221(2) | 0.038(1) | 0.062(2) | 0.0203(9) | 0.002(1) | −0.0024(8) | −0.007(1) |
| C(14) | 2a | 0.7133(2) | 0.1753(1) | 0.6462(2) | 0.0189(7) | 0.0237(8) | 0.0203(7) | −0.0017(6) | 0.0021(6) | 0.0017(6) |
| C(15) | 2a | 0.8123(2) | 0.2297(1) | 0.7408(2) | 0.0215(8) | 0.027(1) | 0.0294(9) | −0.0051(7) | 0.0008(6) | −0.0016(7) |
| C(16) | 2a | 1.0032(2) | 0.2193(1) | 0.7338(2) | 0.0226(9) | 0.037(1) | 0.036(1) | −0.0033(8) | −0.0038(7) | 0.0000(9) |
| C(17) | 2a | 0.7610(2) | 0.1943(1) | 0.5100(2) | 0.0256(9) | 0.044(1) | 0.0236(9) | −0.0052(8) | 0.0066(7) | 0.0051(8) |
| C(18) | 2a | 0.5213(2) | −0.0595(1) | 0.4279(2) | 0.0261(9) | 0.032(1) | 0.0213(8) | −0.0011(7) | 0.0051(6) | −0.0081(7) |
| C(19) | 2a | 0.6750(3) | −0.0223(2) | 0.3682(3) | 0.034(1) | 0.050(1) | 0.046(1) | 0.000(1) | 0.022(1) | −0.002(1) |
| C(20) | 2a | 0.5766(3) | −0.1136(1) | 0.5393(2) | 0.030(1) | 0.029(1) | 0.031(1) | 0.0046(8) | 0.0007(8) | −0.0072(8) |
| C(21) | 2a | 0.1475(3) | −0.1560(1) | 0.7618(2) | 0.046(1) | 0.0206(9) | 0.0294(9) | 0.0018(8) | 0.0145(8) | −0.0009(7) |
| C(22) | 2a | −0.0067(2) | 0.0044(1) | 1.1157(2) | 0.0197(7) | 0.0235(8) | 0.0198(7) | −0.0006(6) | 0.0056(6) | −0.0019(7) |
| C(23) | 2a | −0.0832(3) | −0.0785(1) | 1.0927(2) | 0.043(1) | 0.027(1) | 0.0286(9) | −0.0108(8) | 0.0102(8) | 0.0004(8) |

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