

(2*S*,3*R*,4*R*,5*R*)-3,4-Dihydroxy-5-(hydroxymethyl)pyrrolidine-2-carboxylic acid [(2*S*,3*R*,4*R*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)proline]

Daniel Best,^a Sarah F. Jenkinson,^{a*} Amber L. Thompson,^b David J. Watkin,^b Francis X. Wilson,^c Robert J. Nash^d and George W. J. Fleet^a

^aDepartment of Organic Chemistry, Chemistry Research Laboratory, Department of Chemistry, University of Oxford, Oxford OX1 3TA, England, ^bDepartment of Chemical Crystallography, Chemistry Research Laboratory, Department of Chemistry, University of Oxford, Oxford OX1 3TA, England, ^cSummit PLC, 91 Milton Park, Abingdon, Oxon OX14 4RY, England, and ^dPhytoquest Limited, IBERS, Aberystwyth University, Plas Gogerddan, Aberystwyth SY23 3EB, Ceredigion, Wales
Correspondence e-mail: sarah.jenkinson@chem.ox.ac.uk

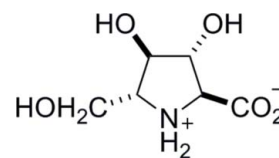
Received 28 August 2009; accepted 3 September 2009

Key indicators: single-crystal X-ray study; *T* = 150 K; mean $\sigma(\text{C}-\text{C}) = 0.003 \text{ \AA}$; *R* factor = 0.027; *wR* factor = 0.066; data-to-parameter ratio = 7.7.

The crystal structure of the title compound, C₆H₁₁NO₅, establishes the relative configuration at the four stereogenic centres; the absolute configuration is determined by the use of D-glucuronolactone as the starting material for the synthesis. Molecules are linked by intermolecular O—H···O and N—H···O hydrogen bonds into a three-dimensional network, with each molecule acting as a donor and acceptor for five hydrogen bonds.

Related literature

For related literature on iminosugars, see: Asano *et al.* (2000); Watson *et al.* (2001). For related literature on pipecolic acids, see: Fleet *et al.* (1987); Booth *et al.* (2007); Bashyal, Chow, Fellows & Fleet (1987); Manning *et al.* (1985); di Bello *et al.* (1984); Yoshimura *et al.* (2008). For related literature on bulgecinine, see: Toumi *et al.* (2008); Bashyal *et al.* (1986); Bashyal, Chow & Fleet (1987); Shinagawa *et al.* (1984, 1985). For related literature on alexines, see: Pereira *et al.* (1991); Donohoe *et al.* (2008); Kato *et al.* (2003); Wormald *et al.* (1998). For absolute configuration, see: Flack (1983); Flack & Bernardinelli (2000); Flack & Shmueli (2007); Hooft *et al.* (2008); Thompson *et al.* (2008); Watkin (1994). For the weighting scheme, see: Prince (1982); Thompson & Watkin (2009).



Experimental

Crystal data

C₆H₁₁NO₅ $\gamma = 102.8244 (19)^\circ$
M_r = 177.16 *V* = 187.50 (2) Å³
 Triclinic, *P*1 *Z* = 1
a = 5.4160 (2) Å Mo *K*α radiation
b = 5.8236 (3) Å $\mu = 0.14 \text{ mm}^{-1}$
c = 6.6006 (3) Å *T* = 150 K
 $\alpha = 102.836 (2)^\circ$ 0.25 × 0.17 × 0.06 mm
 $\beta = 104.776 (2)^\circ$

Data collection

Area diffractometer 2314 measured reflections
 Absorption correction: multi-scan 834 independent reflections
 (*DENZO/SCALEPACK*; 814 reflections with *I* > 2σ(*I*)
 Otwinowski & Minor, 1997) *R_{int}* = 0.025
T_{min} = 0.94, *T_{max}* = 0.99

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.027$ 3 restraints
 $wR(F^2) = 0.066$ H-atom parameters constrained
S = 1.00 $\Delta\rho_{\text{max}} = 0.24 \text{ e \AA}^{-3}$
 834 reflections $\Delta\rho_{\text{min}} = -0.17 \text{ e \AA}^{-3}$
 109 parameters

Table 1

Hydrogen-bond geometry (Å, °).

<i>D</i> —H··· <i>A</i>	<i>D</i> —H	H··· <i>A</i>	<i>D</i> ··· <i>A</i>	<i>D</i> —H··· <i>A</i>
O8—H81···O1 ⁱ	0.83	1.85	2.679 (3)	175
N5—H51···O11 ⁱⁱ	0.88	2.03	2.873 (3)	160
N5—H52···O3 ⁱⁱⁱ	0.89	1.93	2.814 (3)	173
O11—H111···O1 ⁱⁱⁱ	0.82	1.89	2.696 (3)	170
O12—H121···O8 ^{iv}	0.82	1.91	2.668 (3)	154

Symmetry codes: (i) *x* + 1, *y* + 1, *z* + 1; (ii) *x*, *y* + 1, *z*; (iii) *x* + 1, *y*, *z*; (iv) *x* − 1, *y* − 1, *z*.

Data collection: *COLLECT* (Nonius, 2001); cell refinement: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO/SCALEPACK*; program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *CRYSTALS* (Betteridge *et al.*, 2003); molecular graphics: *CAMERON* (Watkin *et al.*, 1996); software used to prepare material for publication: *CRYSTALS*.

Supplementary data and figures for this paper are available from the IUCr electronic archives (Reference: LH2896).

References

Altomare, A., Cascarano, G., Giacovazzo, C., Guagliardi, A., Burla, M. C., Polidori, G. & Camalli, M. (1994). *J. Appl. Cryst.* **27**, 435.
 Asano, N., Nash, R. J., Molyneux, R. J. & Fleet, G. W. J. (2000). *Tetrahedron Asymmetry*, **11**, 1645–1680.
 Bashyal, B. P., Chow, H.-F., Fellows, L. E. & Fleet, G. W. J. (1987). *Tetrahedron*, **43**, 415–422.

- Bashyal, B. P., Chow, H.-F. & Fleet, G. W. J. (1986). *Tetrahedron Lett.* **27**, 3205–3208.
- Bashyal, B. P., Chow, H.-F. & Fleet, G. W. J. (1987). *Tetrahedron*, **43**, 423–430.
- Betteridge, P. W., Carruthers, J. R., Cooper, R. I., Prout, K. & Watkin, D. J. (2003). *J. Appl. Cryst.* **36**, 1487.
- Booth, K. V., Jenkinson, S. F., Watkin, D. J., Sharp, H., Jones, P. W., Nash, R. J. & Fleet, G. W. J. (2007). *Acta Cryst.* **E63**, o3783–o3784.
- di Bello, I. C., Dorling, P., Fellows, L. & Winchester, B. (1984). *FEBS Lett.* **176**, 61–64.
- Donohoe, T. J., Cheeseman, M. D., O’Riordan, T. J. C. & Kershaw, J. A. (2008). *Org. Biomol. Chem.* pp. 3896–3898.
- Flack, H. D. (1983). *Acta Cryst.* **A39**, 876–881.
- Flack, H. D. & Bernardinelli, G. (2000). *J. Appl. Cryst.* **33**, 1143–1148.
- Flack, H. D. & Shmueli, U. (2007). *Acta Cryst.* **A63**, 257–265.
- Fleet, G. W. J., Fellows, L. E. & Smith, P. W. (1987). *Tetrahedron*, **43**, 979–990.
- Hoof, R. W. W., Straver, L. H. & Spek, A. L. (2008). *J. Appl. Cryst.* **41**, 96–103.
- Kato, A., Kano, E., Adachi, I., Molyneux, R. J., Watson, A. A., Nash, R. J., Fleet, G. W. J., Wormald, M. R., Kizu, H., Ikeda, K. & Asano, N. (2003). *Tetrahedron Asymmetry*, **14**, 325–331.
- Manning, K. S., Lynn, D. G., Shabanowitz, J., Fellows, L. E., Singh, M. & Schrire, B. D. (1985). *J. Chem. Soc. Chem. Commun.* pp. 127–129.
- Nonius (2001). *COLLECT*. Nonius BV, Delft, The Netherlands.
- Otwinowski, Z. & Minor, W. (1997). *Methods in Enzymology*, Vol. 276, *Macromolecular Crystallography*, Part A, edited by C. W. Carter Jr & R. M. Sweet, pp. 307–326. New York: Academic Press.
- Pereira, A. C. D., Kaplan, M. A. C., Maia, J. G. S., Gottlieb, O. R., Nash, R. J., Fleet, G., Pearce, L., Watkin, D. J. & Scofield, A. M. (1991). *Tetrahedron*, **47**, 5637–5640.
- Prince, E. (1982). *Mathematical Techniques in Crystallography and Materials Science*. New York: Springer-Verlag.
- Shinagawa, S., Kasahara, F., Harada, S. & Asai, M. (1984). *Tetrahedron*, **40**, 3465–3470.
- Shinagawa, S., Maki, M., Kintaka, K., Imada, A. & Asai, M. (1985). *J. Antibiot.* **38**, 17–23.
- Thompson, A. L. & Watkin, D. J. (2009). *Tetrahedron Asymmetry*, **20**, 712–717.
- Thompson, A. L., Watkin, D. J., Gal, Z. A., Jones, L., Hollinshead, J., Jenkinson, S. F., Fleet, G. W. J. & Nash, R. J. (2008). *Acta Cryst.* **C64**, o649–o652.
- Toumi, M., Couty, F. & Evano, G. (2008). *Tetrahedron Lett.* **49**, 1175–1179.
- Watkin, D. (1994). *Acta Cryst.* **A50**, 411–437.
- Watkin, D. J., Prout, C. K. & Pearce, L. J. (1996). *CAMERON*. Chemical Crystallography Laboratory, Oxford, England.
- Watson, A. A., Fleet, G. W. J., Asano, N., Molyneux, R. J. & Nash, R. J. (2001). *Phytochemistry*, **56**, 265–295.
- Wormald, M. R., Nash, R. J., Hrnčiar, P., White, J. D., Molyneux, R. J. & Fleet, G. W. J. (1998). *Tetrahedron Asymmetry*, **9**, 2549–2558.
- Yoshimura, Y., Ohara, C., Imahori, T., Saito, Y., Kato, A., Miyauchi, S., Adachi, I. & Takahata, H. (2008). *Bioorg. Med. Chem.* **16**, 8273–8286.

supplementary materials

Acta Cryst. (2009). E65, o2418-o2419 [doi:10.1107/S1600536809035636]

(2*S*,3*R*,4*R*,5*R*)-3,4-Dihydroxy-5-(hydroxymethyl)pyrrolidine-2-carboxylic acid [(2*S*,3*R*,4*R*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)proline]

D. Best, S. F. Jenkinson, A. L. Thompson, D. J. Watkin, F. X. Wilson, R. J. Nash and G. W. J. Fleet

Comment

This paper firmly establishes the structure of the trihydroxyproline **1** (Fig. 1), the amino acid corresponding to DMDP **2**. There are over 100 iminosugars that have been isolated as natural products [such as DMDP **2** and DNJ **4**] that are the equivalent of carbohydrates with the ring oxygen replaced by nitrogen (Asano *et al.*, 2000; Watson *et al.*, 2001). In contrast, the pipercolic acid BR1 **3** [related to DNJ **4** in the same way as **1** to **2**] (Fleet *et al.*, 1987; Booth *et al.*, 2007; Bashyal, Chow, Fellows & Fleet, 1987) is among the rare examples of naturally occurring amino acid sugar analogues. BR1 **3** was isolated from the seeds of *Baphia racemosa* (Manning *et al.*, 1985) and is an inhibitor of glucuronidase and iduronidase (di Bello *et al.*, 1984; Yoshimura *et al.*, 2008). Bulgecinine **5** (Toumi *et al.*, 2008; Bashyal *et al.*, 1986; Bashyal, Chow & Fleet, 1987), a deoxy analogue of **1**, is a constituent of the bulgecin glycopeptide antibiotics (Shinagawa *et al.*, 1984; Shinagawa *et al.*, 1985). 7a-Epialexaflorine **6**, isolated from the leaves of *Alexa grandiflora* (Pereira *et al.*, 1991), is the only example of an amino acid analogue of the alexines (Donohoe *et al.*, 2008; Kato *et al.*, 2003; Wormald *et al.*, 1998).

The title compound (Fig. 2) was seen to adopt an envelope conformation with C4 out of the plane. The absolute configuration was determined by the use of D-glucuronolactone as the starting material for the synthesis. The molecule exists as an extensively hydrogen bonded network with each molecule acting as a donor and acceptor for 5 hydrogen bonds (Fig. 3, Fig. 4). Only classical hydrogen bonding has been considered.

Experimental

The title compound was recrystallized from a mixture of hot ethanol and water: m.p. 449 K - decomposed; $[\alpha]_D^{25} +14.7$ (*c*, 1.13 in H₂O).

Refinement

Initial refinement of the Flack *x* parameter gave a value of -0.5 (10), suggesting that the absolute configuration could not be determined (Flack, 1983; Flack & Bernardinelli, 2000). Analysis of the Bijvoet differences using *CRYSTALS* gave the Hooft *y* parameter as -0.2 (7), and the probability the configuration is correct assuming the material is enantiopure was determined to be 78.7% (Hooft *et al.*, 2008; Thompson *et al.* 2008; Thompson & Watkin 2009). In the absence of significant anomalous scattering (FRIEDIF = 6.71; Flack & Shmueli, 2007), Friedel pairs were merged for the final refinement.

The H atoms were all located in a difference map, but those attached to carbon atoms were repositioned geometrically. The H atoms were initially refined with soft restraints on the bond lengths and angles to regularize their geometry (C—H in the range 0.93–0.98, N—H in the range 0.86–0.89 N—H to 0.86 O—H = 0.82 Å) and $U_{\text{iso}}(\text{H})$ (in the range 1.2–1.5 times U_{eq} of the parent atom), after which the positions were refined with riding constraints.

Figures



Fig. 1. Synthetic scheme.

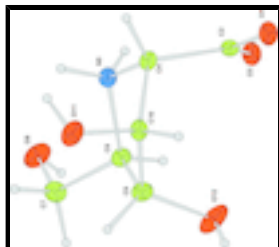


Fig. 2. The title compound with displacement ellipsoids drawn at the 50% probability level. H atoms are shown as spheres of arbitrary radius.

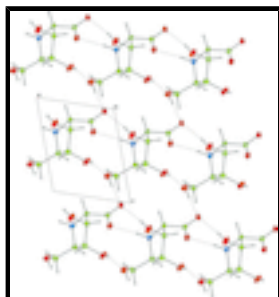


Fig. 3. Packing diagram for the title compound projected along the *b*-axis.

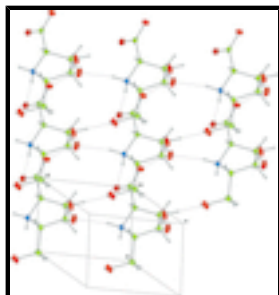


Fig. 4. Packing diagram for the title compound. The compound exists as an extensively hydrogen bonded network.

(2*S*,3*R*,4*R*,5*R*)-3,4-Dihydroxy-5-(hydroxymethyl)pyrrolidine-2-carboxylic acid

Crystal data

$C_6H_{11}NO_5$

$M_r = 177.16$

Triclinic, *P*1

Hall symbol: P 1

$a = 5.4160$ (2) Å

$b = 5.8236$ (3) Å

$c = 6.6006$ (3) Å

$\alpha = 102.836$ (2)°

$\beta = 104.776$ (2)°

$\gamma = 102.8244$ (19)°

$V = 187.504$ (15) Å³

$Z = 1$

$F_{000} = 94$

$D_x = 1.569$ Mg m⁻³

Melting point: not measured K

Mo *K*α radiation, $\lambda = 0.71073$ Å

Cell parameters from 696 reflections

$\theta = 5-27^\circ$

$\mu = 0.14$ mm⁻¹

$T = 150$ K

Plate, clear_pale_colourless

0.25 × 0.17 × 0.06 mm

Data collection

Area diffractometer	814 reflections with $I > 2\sigma(I)$
Monochromator: graphite	$R_{\text{int}} = 0.025$
$T = 150$ K	$\theta_{\text{max}} = 27.5^\circ$
ω scans	$\theta_{\text{min}} = 5.6^\circ$
Absorption correction: multi-scan (DENZO/SCALEPACK; Otwinowski & Minor, 1997)	$h = -7 \rightarrow 7$
$T_{\text{min}} = 0.94$, $T_{\text{max}} = 0.99$	$k = -6 \rightarrow 7$
2314 measured reflections	$l = -8 \rightarrow 7$
834 independent reflections	

Refinement

Refinement on F^2	Primary atom site location: structure-invariant direct methods
Least-squares matrix: full	Hydrogen site location: inferred from neighbouring sites
$R[F^2 > 2\sigma(F^2)] = 0.027$	H-atom parameters constrained
$wR(F^2) = 0.066$	Method, part 1, Chebychev polynomial, (Watkin, 1994, Prince, 1982) [weight] = $1.0/[A_0 * T_0(x) + A_1 * T_1(x) \dots + A_{n-1} * T_{n-1}(x)]$ where A_i are the Chebychev coefficients listed below and $x = F / F_{\text{max}}$ Method = Robust Weighting (Prince, 1982) $W = [\text{weight}] * [1 - (\Delta F / 6 * \text{sigma}(\Delta F))^2]^2$ A_i are: 22.5 35.8 21.7 10.1 2.91
$S = 1.00$	$(\Delta/\sigma)_{\text{max}} = 0.0001$
834 reflections	$\Delta\rho_{\text{max}} = 0.24 \text{ e } \text{\AA}^{-3}$
109 parameters	$\Delta\rho_{\text{min}} = -0.17 \text{ e } \text{\AA}^{-3}$
3 restraints	Extinction correction: None

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (\AA^2)

	<i>x</i>	<i>y</i>	<i>z</i>	$U_{\text{iso}}^*/U_{\text{eq}}$
O1	0.1323 (3)	0.4021 (3)	0.0397 (3)	0.0170
C2	0.3330 (4)	0.5769 (4)	0.1694 (3)	0.0124
O3	0.3285 (3)	0.7782 (3)	0.2816 (3)	0.0161
C4	0.6067 (4)	0.5299 (3)	0.1892 (3)	0.0118
N5	0.8297 (3)	0.7483 (3)	0.3462 (3)	0.0120
C6	0.8425 (4)	0.7309 (4)	0.5744 (3)	0.0130
C7	1.1277 (4)	0.8313 (4)	0.7284 (3)	0.0167
O8	1.2417 (3)	1.0809 (3)	0.7415 (3)	0.0209
C9	0.7092 (4)	0.4584 (4)	0.5443 (3)	0.0150
C10	0.6269 (4)	0.3243 (4)	0.2968 (3)	0.0135
O11	0.8192 (3)	0.2063 (3)	0.2544 (3)	0.0229
O12	0.4844 (4)	0.4511 (3)	0.6175 (3)	0.0252

supplementary materials

H41	0.6365	0.4960	0.0477	0.0144*
H61	0.7333	0.8262	0.6278	0.0169*
H72	1.1284	0.8203	0.8747	0.0191*
H71	1.2343	0.7354	0.6770	0.0194*
H91	0.8360	0.3904	0.6257	0.0183*
H101	0.4566	0.2013	0.2549	0.0154*
H81	1.2048	1.1744	0.8368	0.0313*
H51	0.7954	0.8869	0.3332	0.0177*
H52	0.9817	0.7443	0.3204	0.0178*
H111	0.8993	0.2734	0.1839	0.0347*
H121	0.4206	0.3112	0.6224	0.0383*

Atomic displacement parameters (\AA^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0115 (7)	0.0187 (7)	0.0178 (7)	0.0024 (5)	0.0034 (5)	0.0030 (6)
C2	0.0128 (9)	0.0137 (9)	0.0134 (9)	0.0052 (7)	0.0051 (7)	0.0074 (7)
O3	0.0153 (7)	0.0148 (7)	0.0210 (7)	0.0075 (6)	0.0074 (5)	0.0057 (6)
C4	0.0113 (9)	0.0115 (8)	0.0130 (9)	0.0032 (7)	0.0050 (7)	0.0032 (7)
N5	0.0123 (8)	0.0098 (7)	0.0150 (8)	0.0039 (6)	0.0052 (6)	0.0042 (6)
C6	0.0142 (9)	0.0115 (8)	0.0136 (9)	0.0030 (7)	0.0053 (7)	0.0041 (7)
C7	0.0154 (9)	0.0161 (9)	0.0152 (9)	0.0013 (8)	0.0023 (7)	0.0042 (8)
O8	0.0246 (8)	0.0151 (8)	0.0190 (7)	-0.0019 (6)	0.0100 (6)	0.0020 (6)
C9	0.0173 (10)	0.0130 (9)	0.0165 (10)	0.0042 (7)	0.0066 (8)	0.0067 (7)
C10	0.0121 (9)	0.0124 (9)	0.0176 (9)	0.0049 (7)	0.0058 (7)	0.0050 (7)
O11	0.0280 (8)	0.0223 (8)	0.0356 (9)	0.0180 (7)	0.0218 (7)	0.0179 (7)
O12	0.0325 (9)	0.0164 (7)	0.0304 (9)	0.0018 (7)	0.0222 (8)	0.0056 (7)

Geometric parameters (\AA , $^\circ$)

O1—C2	1.264 (3)	C7—O8	1.421 (2)
C2—O3	1.249 (2)	C7—H72	0.981
C2—C4	1.545 (2)	C7—H71	0.959
C4—N5	1.498 (2)	O8—H81	0.832
C4—C10	1.532 (3)	C9—C10	1.545 (3)
C4—H41	0.972	C9—O12	1.415 (2)
N5—C6	1.517 (2)	C9—H91	0.972
N5—H51	0.885	C10—O11	1.420 (2)
N5—H52	0.886	C10—H101	0.963
C6—C7	1.515 (3)	O11—H111	0.816
C6—C9	1.535 (3)	O12—H121	0.823
C6—H61	0.973		
O1—C2—O3	126.24 (18)	C6—C7—O8	111.22 (16)
O1—C2—C4	115.43 (17)	C6—C7—H72	108.8
O3—C2—C4	118.32 (17)	O8—C7—H72	109.4
C2—C4—N5	110.92 (15)	C6—C7—H71	109.8
C2—C4—C10	109.46 (14)	O8—C7—H71	108.5
N5—C4—C10	103.55 (15)	H72—C7—H71	109.1

C2—C4—H41	111.2	C7—O8—H81	110.0
N5—C4—H41	108.5	C6—C9—C10	106.41 (15)
C10—C4—H41	113.0	C6—C9—O12	106.33 (16)
C4—N5—C6	106.33 (14)	C10—C9—O12	111.81 (16)
C4—N5—H51	110.5	C6—C9—H91	110.0
C6—N5—H51	109.1	C10—C9—H91	109.3
C4—N5—H52	109.8	O12—C9—H91	112.7
C6—N5—H52	111.2	C9—C10—C4	103.65 (15)
H51—N5—H52	109.8	C9—C10—O11	109.89 (16)
N5—C6—C7	110.92 (15)	C4—C10—O11	113.98 (15)
N5—C6—C9	105.61 (15)	C9—C10—H101	108.3
C7—C6—C9	114.30 (16)	C4—C10—H101	111.8
N5—C6—H61	108.0	O11—C10—H101	109.0
C7—C6—H61	109.9	C10—O11—H111	110.0
C9—C6—H61	107.9	C9—O12—H121	109.5

Hydrogen-bond geometry (\AA , $^\circ$)

<i>D</i> —H \cdots <i>A</i>	<i>D</i> —H	H \cdots <i>A</i>	<i>D</i> \cdots <i>A</i>	<i>D</i> —H \cdots <i>A</i>
C7—H71 \cdots O12 ⁱ	0.96	2.39	3.328 (3)	166
C10—H101 \cdots O3 ⁱⁱ	0.96	2.47	3.199 (3)	133
O8—H81 \cdots O1 ⁱⁱⁱ	0.83	1.85	2.679 (3)	175
N5—H51 \cdots O11 ^{iv}	0.88	2.03	2.873 (3)	160
N5—H52 \cdots O3 ⁱ	0.89	1.93	2.814 (3)	173
O11—H111 \cdots O1 ⁱ	0.82	1.89	2.696 (3)	170
O12—H121 \cdots O8 ^v	0.82	1.91	2.668 (3)	154

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

Fig. 1

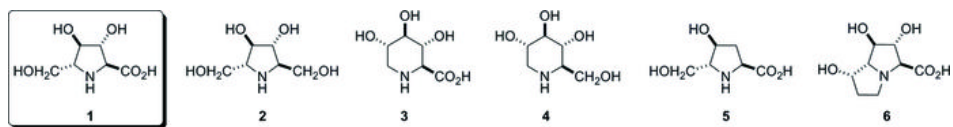


Fig. 2

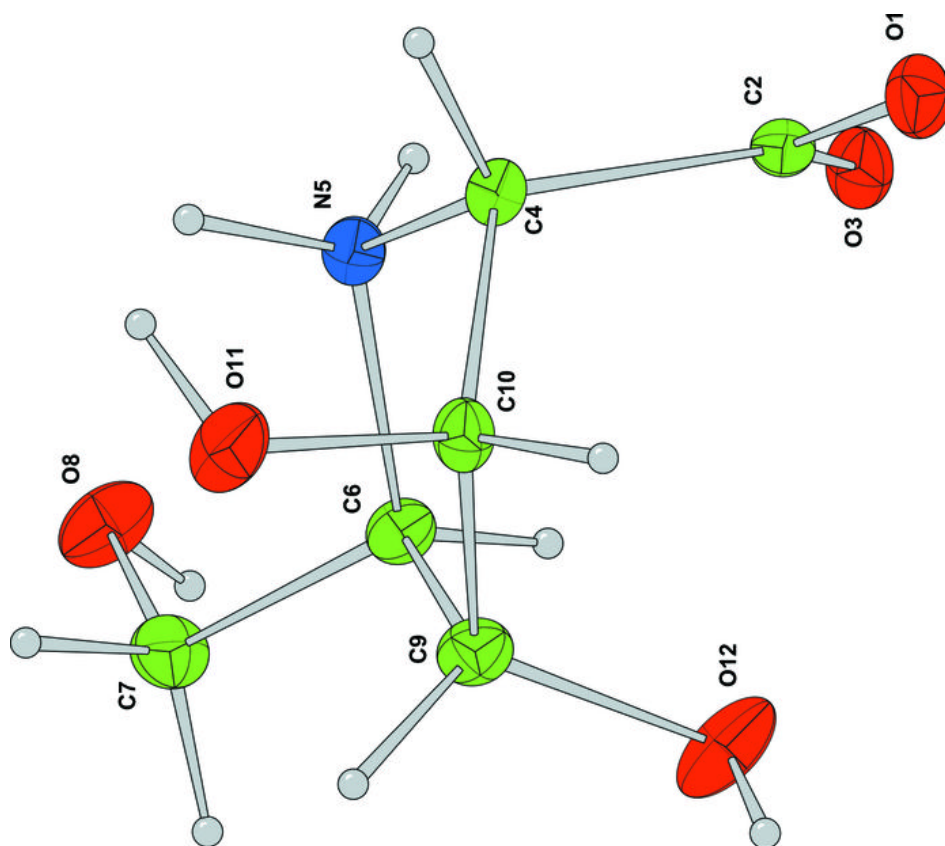


Fig. 3

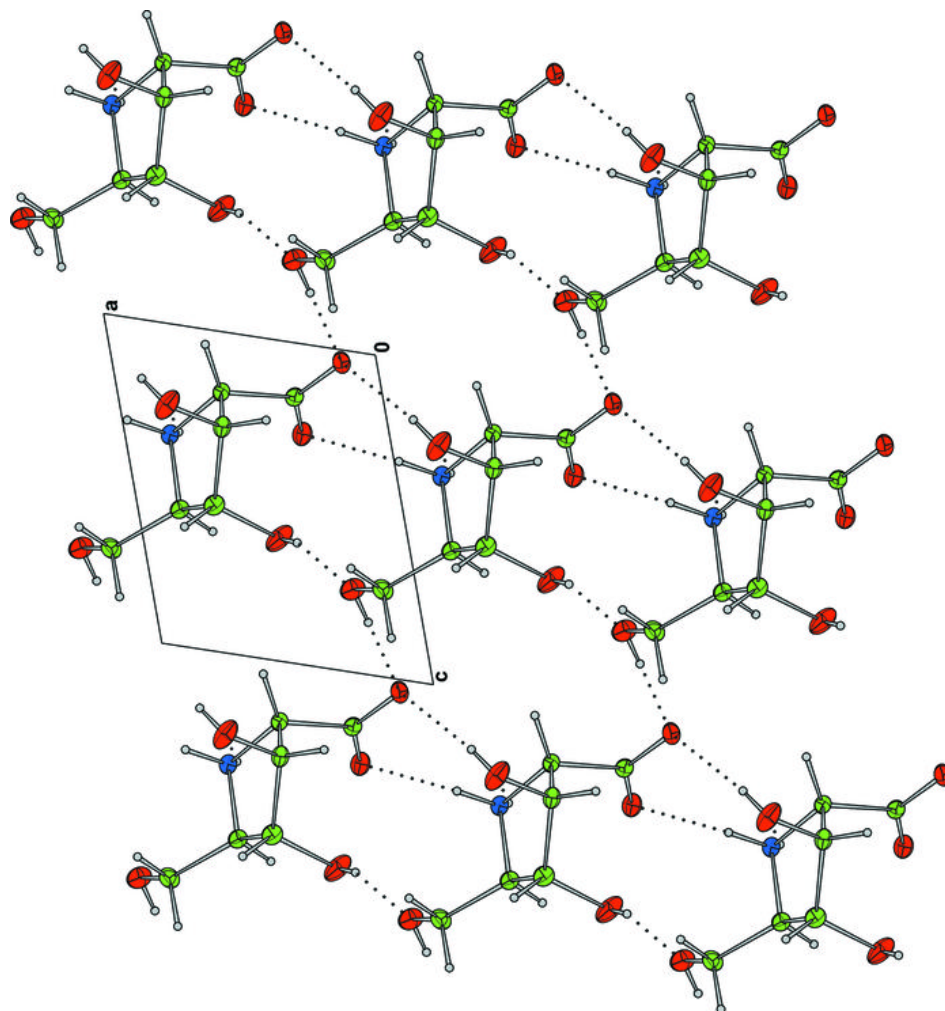


Fig. 4

