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(2*S*,4*R*)-1-Benzyl 2-*tert*-butyl 4-[*N*,*N*′-bis(*tert*-butyloxycarbonyl)hydrazino]-5-oxopyrrolidine-1,2-dicarboxylate

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Key indicators

Single-crystal X-ray study
T = 293 K
Mean σ(C–C) = 0.012 Å
R factor = 0.052
wR factor = 0.158
Data-to-parameter ratio = 7.8

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

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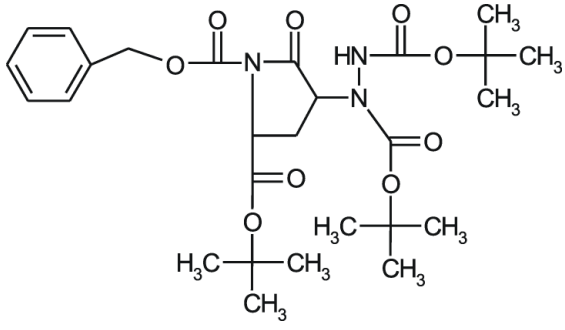
The title compound, $C_{27}H_{39}N_3O_9$, is a key intermediate in the synthesis of novel β-turn mimetics based on electrophilic amination of enantiomerically pure (*S*)-pyroglutamic acid. The molecule adopts an extended conformation which is not stabilized by either intra- or intermolecular hydrogen bonding. The pyrrolidine five-membered ring adopts an envelope conformation, with the unsubstituted C atom situated at the flap and the other four atoms almost coplanar.

Comment

The presence of *N*-methyl amino acids and proline residues in naturally occurring peptides may cause *cis–trans* isomerization of the amide bond and lead to conformational changes, which are important for molecular recognition (Dugave & Demange, 2003). The significance of *cis*-amide bonds for peptide bioactivity led to the synthesis of several surrogates of amino acids, which were able to lock the peptide bond in the *cis*-geometry (Dumy *et al.*, 1997; Keller *et al.*, 1998; Mutter *et al.*, 1999; Tuchscherer & Mutter, 2001). In particular, Paul *et al.* (1992) designed mimetics of the *cis*-peptide bond based on extension at C^{γ} of the pyroglutamic acid residue. Their preliminary computer modelling data suggested that, depending on the configuration at both chiral centres, these should stand for either VIa or VIb β-turn mimetics. In contrast with a tetrazole replacement for the peptide bond (Zabrocki *et al.*, 1988), the pyroglutamic acid derivatives are more rigid (Kaczmarek, 2003). Moreover, their carboxylic acid group could be either a donor or an acceptor of hydrogen bonds, without affecting the polypeptide main-chain amide moieties.



(I)

The title compound, (I), is a key intermediate in the synthesis of novel β-turn mimetics based on electrophilic amination of enantiomerically pure (*S*)-pyroglutamic acid (Kaczmarek *et al.*, 1999). A view of (I) with the atom labels is given in Fig. 1.

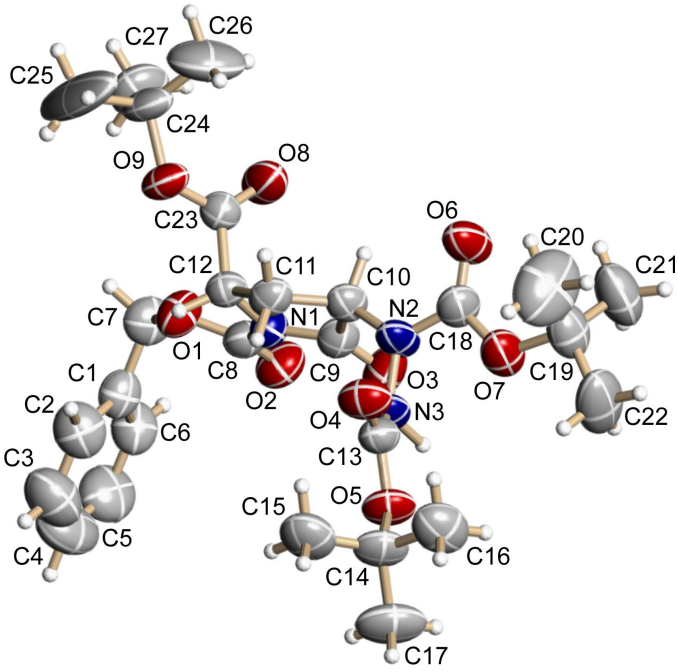


Figure 1
The molecular structure of (I). Displacement ellipsoids are drawn at the 50% probability level.

The molecule has two chiral centres, *viz*. C10 and C12. Their absolute configurations follow from the synthetic procedure and are *R* and *S*, respectively. The molecule adopts an extended conformation which is not stabilized by either intra- or intermolecular hydrogen bonding. This is quite an unusual situation, because in (I) the only H atom prone to hydrogen bonding (*i.e.* hydrazone atom H3) is confronted with potentially 11 O- and N-atom acceptors.

The terminal benzyloxycarbonyl (*Z*) and two *tert*-butoxycarbonyl (Boc) groups are connected to the central 4-hydrazonopyrrolidine fragment with pseudo-peptide bonds. Torsion angles defining the conformation along these bonds are summarized in Table 1. All pseudo-peptide bonds deviate significantly from planarity. The largest deviation from planarity exists in the N2—N3—C14—O5 system. Atom N3 adopts a tetrahedral configuration, as indicated by the sum of the respective bond angles (346°). The negative atomic charge at atom N3 (−0.71 e) is larger than those at the remaining two N atoms, N1 and N2, at −0.51 and −0.40 e, respectively. Atomic charges are derived from electrostatic potentials and were calculated using *GAUSSIAN03* (Frisch *et al.*, 2003) at the MP2/6-31+G(*d*,*p*) level for the X-ray determined coordinates. Grid points were selected according to the *CHELPG* procedure of Breneman & Wiberg (1990). This suggests that the N3 lone pair is only partially involved in the electron-density delocalization and is mainly located on the N atom. The N3—C13 bond is longer than the corresponding N2—C18 bond. Also, the N2—N3 bond is much longer than the standard double bond (1.240 Å) and is quite close to the single bond observed in the (C,H)—N—N—(C,H) system with one planar and one pyramidal N atom (1.42 Å; Allen *et al.*, 1992). Atom N1 is coplanar with the two neighbouring carbonyl groups. Its negative atomic charge is smaller than that of the tetrahedral atom N3 and suggests that the electron density is delocalized over the O2—C8—N1—C9—O3 molecular fragment.

The pyrrolidine five-membered ring adopts an envelope conformation, with atoms N1, C9, C10 and C12 almost coplanar and atom C11 situated at the flap. The three lowest ring asymmetry parameters (Griffin *et al.*, 1984) are C_S(C11) = 1.4 (6), C_2(N1) = 13.8 (6) and C_2(C9) = 17.2 (6)°. The N-terminal benzyloxycarbonyl (*Z*)-group adopts the sterically less favoured *gauche* conformation (Benedetti *et al.*, 1983). The phenyl rings are located too far from one another for stacking interactions.

The crystal packing is loose (D_m = 1.17 M gm^{-3}) and is not strengthened by intramolecular hydrogen bonding. Molecules are oriented in such a way that their longest dimension is approximately parallel to the crystallographic *c* axis.

Experimental

The title compound was synthesized by the electrophilic amination of enantiomerically pure (*S*)-pyroglutamic acid (Kaczmarek *et al.*, 1999). The crystal used for data collection was obtained by vapour diffusion; the sample was dissolved in methanol and equilibrated at room temperature against a 2:1 mixture of water and methanol for 12 d.

Crystal data

$C_{27}H_{39}N_3O_9$
M_r = 549.61
Monoclinic, $P2_1$
a = 9.883 (2) Å
b = 10.103 (2) Å
c = 15.892 (2) Å
β = 106.59 (1)°
V = 1520.7 (5) Å^3
Z = 2
D_x = 1.200 Mg m^{-3}
D_m = 1.17 Mg m^{-3}
Cu *Kα* radiation
Cell parameters from 90 reflections
θ = 5–12°
μ = 0.75 mm^{-1}
T = 293 (2) K
Prism, colourless
0.5 × 0.2 × 0.1 mm

Data collection

Kuma KM-4 diffractometer
ω–2θ scans
Absorption correction: ψ scan (*XPREP* in *SHELXTL*; Bruker, 2003)
T_{min} = 0.835, T_{max} = 0.928
3512 measured reflections
2805 independent reflections
1442 reflections with $I > 2\sigma(I)$
R_{int} = 0.058
θ_{max} = 70.0°
h = −12 → 11
k = −12 → 1
l = −1 → 19
3 standard reflections
every 100 reflections
intensity decay: 3%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.052
$wR(F^2)$ = 0.158
S = 1.09
2805 reflections
358 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0812P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.24 e Å^{-3}
$\Delta\rho_{min}$ = −0.27 e Å^{-3}
Extinction correction: *SHELXTL*
Extinction coefficient: 0.0125 (14)

Table 1
Selected geometric parameters (Å, °).

O1—C8	1.322 (8)	N1—C8	1.404 (8)
O2—C8	1.196 (8)	N1—C12	1.476 (8)
O3—C9	1.225 (8)	N2—C18	1.355 (7)
O4—C13	1.167 (8)	N2—N3	1.404 (6)
O5—C13	1.354 (7)	N2—C10	1.436 (7)
O6—C18	1.206 (7)	N3—C13	1.386 (8)
O7—C18	1.323 (7)	C9—C10	1.502 (9)
O8—C23	1.207 (7)	C10—C11	1.518 (9)
O9—C23	1.290 (7)	C11—C12	1.521 (8)
N1—C9	1.370 (8)	C12—C23	1.523 (8)
O1—C8—N1—C12	−4.0 (7)	C9—C10—N2—C18	117.9 (6)
O1—C8—N1—C9	−169.1 (5)	N2—N3—C13—O5	−164.3 (5)
C8—N1—C12—C11	174.9 (5)	N3—C13—O5—C14	−178.2 (5)
C8—N1—C12—C23	−67.0 (7)	C10—N2—N3—C13	−122.1 (6)
C8—N1—C9—O3	−17.0 (9)	C1—C7—O1—C8	80.3 (7)
C8—N1—C9—C10	165.3 (5)	N1—C9—C10—C11	20.0 (5)
N1—C12—C23—O9	157.4 (5)	C9—C10—C11—C12	−30.3 (5)
C12—C23—O9—C24	178.4 (5)	C10—C11—C12—N1	29.4 (5)
O7—C18—N2—C10	−168.5 (6)	C11—C12—N1—C9	−18.2 (6)
N2—C18—O7—C19	−171.6 (6)	C12—N1—C9—C10	−1.1 (6)

All H atoms except those of terminal methyl groups were located in a difference Fourier map calculated after three cycles of anisotropic refinement. The latter were placed in calculated positions. The positional and isotropic parameters of H3 were allowed to refine freely. The positional parameters of all remaining H atoms were constrained, with C—H distances in the range 0.93–0.97 Å and $U_{iso}(H) = 1.2U_{eq}(C)$. In the absence of significant anomalous scattering effects, Friedel pairs were merged. The absolute configuration is assumed from the synthesis.

Data collection: *KM-4 Software* (Kuma, 1991); cell refinement: *KM-4 Software*; data reduction: *DATAPROC* (Kuma, 1995); program(s) used to solve structure: *SHELXTL* (Bruker, 2003); program(s) used to refine structure: *SHELXTL*; molecular graphics: *SHELXTL*; software used to prepare material for publication: *SHELXTL*.

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References

Allen, F. H., Kennard, O., Watson, D. G., Brammer, L., Orpen, A. G. & Taylor, R. (1992). *International Tables for Crystallography*, Vol. C, edited by A. J. C. Wilson, pp. 691–705. Dordrecht: Kluwer.

Benedetti, E., Pedone, C., Toniolo, C., Dudek, M., Némethy, G. & Scheraga, H. A. (1983). *Int. J. Peptide Res.* **21**, 163–181.

Breneman, C. M. & Wiberg, K. B. (1990). *J. Comput. Chem.* **11**, 361–373.

Bruker (2003). *SHELXTL*. Version 6.14. Bruker AXS Inc., Madison, Wisconsin, USA.

Dugave, Ch. & Demange, L. (2003). *Chem. Rev.* **103**, 2475–2532.

Dumy, P., Keller, M., Ryan, D. E., Rohwedder, B., Wöhr, T. & Mutter, M. (1997). *J. Am. Chem. Soc.* **119**, 918–925.

Frisch, M. J., Trucks, G. W., Schlegel, H. B., Scuseria, G. E., Robb, M. A., Cheeseman, J. R., Montgomery, J. A., Vreven, T. Jr, Kudin, K. N., Burant, J. C., Millam, J. M., Iyengar, S. S., Tomasi, J., Barone, V. *et al.* (2003). *GAUSSIAN03*. Revision A.1. Gaussian Inc., Pittsburgh, PA, USA.

Griffin, J. F., Duax, W. L. & Weeks, C. M. (1984). *Atlas of Steroid Structure*, Vol. 2, p. 8. New York: IFI/Plenum.

Kaczmarek, K., Zabrocki, J., Łachwa, M. & Lipkowski, A. (1999). *Peptides 1998*, edited by S. Bajusz & F. Hudecz, pp. 668–669. Budapest: Akademia Kiado.

Kaczmarek, K. (2003). Unpublished results.

Keller, M., Sager, C., Dumy, P., Schutkowski, M., Fischer, G. S. & Mutter, M. (1998). *J. Am. Chem. Soc.* **120**, 2714–2720.

Kuma (1991). *KM-4 Software User's Guide*. Version 3.2. Kuma Diffraction, Wrocław, Poland.

Kuma (1995). *DATAPROC*. Version 9.0. Kuma Diffraction, Wrocław, Poland.

Mutter, M., Wöhr, T., Gioria, S. & Keller, M. (1999). *Biopolymers* (Peptide *Sci.*), **51**, 121–128.

Paul, P. K. C., Burney, P. A., Campbell, M. M. & Osguthorpe, D. J. (1992). *Bioorg. Med. Chem. Lett.* **2**, 141–144.

Tuchscherer, G. & Mutter, M. (2001), *Chimia*, **55**, 306–313.

Zabrocki, J., Smith, G. D., Dunbar, J. B., Ijima, H. & Marshall, G. R. (1988). *J. Am. Chem. Soc.* **110**, 5875–5880.