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(1′*S*,2*R*,3*S*,4*S*)-Ethyl 2-hydroxy-4-methyl-3-(1′-phenylethylcarbamoyl)hexanoate

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Key indicators

Single-crystal X-ray study
T = 120 K
Mean σ(C–C) = 0.004 Å
Disorder in main residue
R factor = 0.050
wR factor = 0.126
Data-to-parameter ratio = 11.6

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

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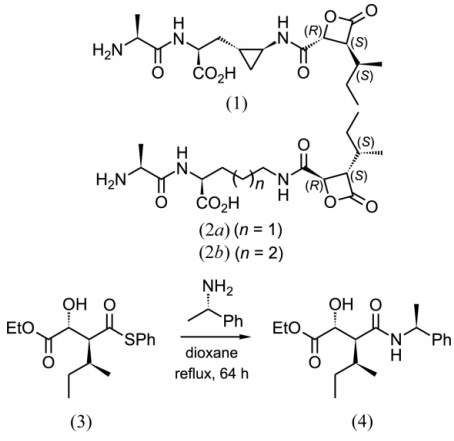
The relative configuration of the title compound, $C_{18}H_{27}NO_4$, was determined as being *R,S,S,S*. There are three crystallographically independent molecules in the asymmetric unit, which show only slight conformational differences. Molecules in the crystal structure are connected by hydrogen bonds in ribbons along the *a* axis.

Comment

Appropriate derivatives of the new natural products belactosins A, (1), C, (2*a*), and its homo-analogue, (2*b*) (see scheme), are highly active proteasome inhibitors (Asai *et al.*, 2000, 2004, Mizukami *et al.*, 1997), which show an impressive potential against some types of cancer and inflammatory diseases (Gillessen *et al.*, 2002; Almond & Cohen, 2002; Elliot *et al.*, 2003). In continuation of our search for synthetic approaches to enantioselective total syntheses of belactosins (Brandl *et al.*, 2000) a precursor of the β-lactone moiety (3) was prepared (Larionov & de Meijere, 2004). The absolute configuration of the β-lactone cycle of the natural products (1)–(3) is (2*R*,3*S*,4*S*), so it was crucial to establish the relative configuration of these centres in (3). Unfortunately, compound (3) is liquid under ambient conditions and a crystalline derivative of (3) had to be prepared. After some experiments, the solid amide (4) was obtained by the reaction of (3) with (*S*)-α-phenylethylamine (see scheme). The X-ray crystal structure of amide (4) is reported in this paper.



There are three independent molecules of (4) in the asymmetric unit (Fig. 1). They all have the same configuration at their chiral centres, but differ by the orientation of the ethyl groups (C11) and phenyl rings (Fig. 2). The absolute configuration of the compound was assigned on the basis of the known *S* configuration of the α-phenylethylamine, used in the

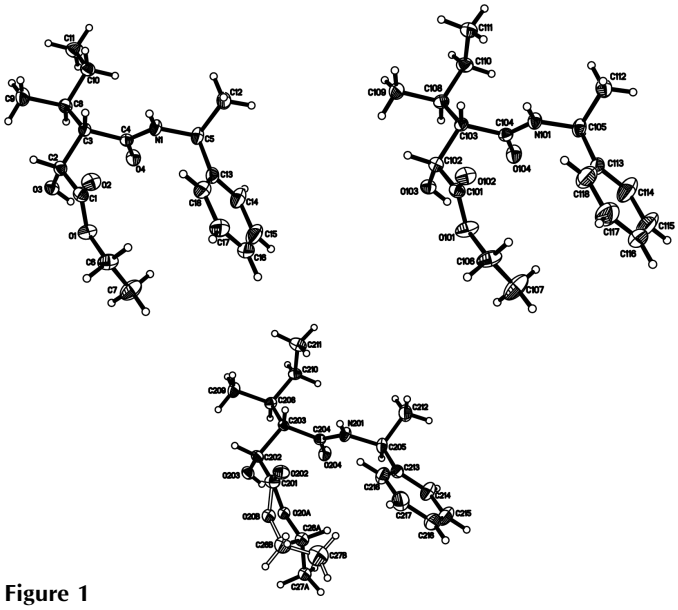


Figure 1
The molecular structure of the three independent molecules of (4) and the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level.

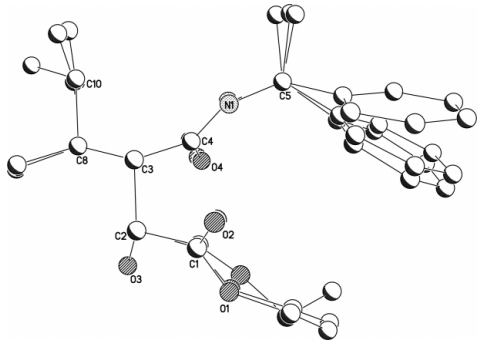


Figure 2
A least-squares superposition of the independent molecules. H atoms and one of the disordered ethoxy groups have been omitted for clarity.

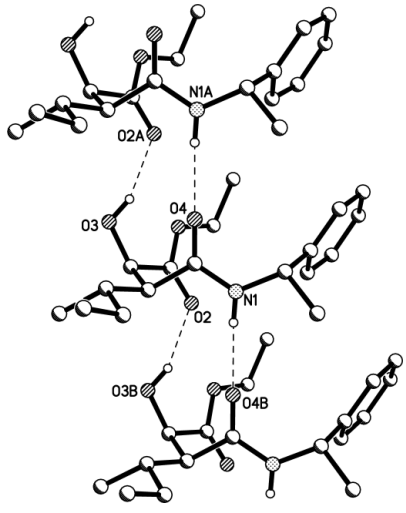


Figure 3
Fragment of the hydrogen-bonded ribbon in the structure of (4). Suffixes *A* and *B* correspond to symmetry codes (ii) and (i), respectively, in Table 1.

synthesis of (4). The terminal ethoxy group of one of the molecules is disordered over two positions; the atoms of the

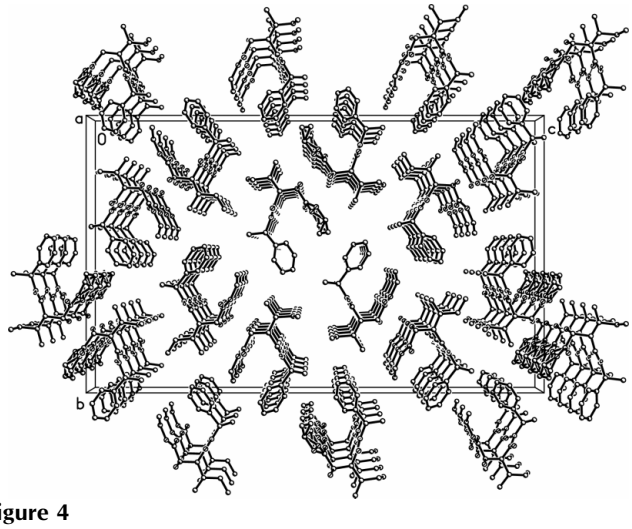


Figure 4
Packing of the molecules (4) in the crystal structure, viewed along the *a* axis, H atoms have been omitted for clarity.

ethoxy groups in the other two molecules also show high anisotropic displacement parameters and are probably also slightly disordered. The molecular geometry of (4) does not reveal any remarkable features. In the crystal structure, the molecules are linked together by pairs of strong O1—H···O2 and N1—H···O4 hydrogen bonds (Fig. 3 and Table 1), forming ribbons which are parallel to the **a** direction (Fig. 4). Each ribbon is composed of one of the crystallographically independent molecules and its symmetry-equivalents.

Experimental

Crystals of (4) suitable for the X-ray experiment were obtained by slow evaporation of a solution in EtOAc–hexane

Crystal data

$C_{18}H_{27}NO_4$
M_r = 321.41
Orthorhombic, $P2_12_12_1$
a = 5.04730 (1) Å
b = 25.1504 (5) Å
c = 41.4912 (9) Å
V = 5266.96 (19) Å^3
Z = 12
D_x = 1.216 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 7902 reflections
θ = 2.5–29.1°
μ = 0.09 mm^{-1}
T = 120 (2) K
Prism, colourless
0.46 × 0.16 × 0.14 mm

Data collection

Bruker SMART 6000 CCD diffractometer
ω scans
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1996)
T_{min} = 0.961, T_{max} = 0.988
44 787 measured reflections
7254 independent reflections
6485 reflections with $I > 2\sigma(I)$
R_{int} = 0.039
θ_{max} = 28.0°
$h = -6 \rightarrow 6$
$k = -31 \rightarrow 33$
$l = -54 \rightarrow 54$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.050
$wR(F^2)$ = 0.126
S = 1.15
7254 reflections
628 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.05P)^2 + 2.5P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.29 e Å^{-3}
$\Delta\rho_{min}$ = −0.20 e Å^{-3}

Table 1
Hydrogen-bonding geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1A···O4^{i}	0.88	2.10	2.978 (3)	176
O3—H3···O2^{ii}	0.84 (4)	2.02 (4)	2.809 (3)	156 (3)
N101—H10C···O104^{i}	0.88	2.10	2.977 (3)	176
O103—H10D···O102^{ii}	0.80 (4)	2.08 (4)	2.808 (3)	152 (4)
N201—H20A···O204^{ii}	0.88	2.13	3.004 (3)	175
O203—H20B···O202^{i}	0.75 (4)	2.09 (4)	2.795 (3)	158 (4)

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

All H atoms were located in difference Fourier maps and included in the refinement in the riding mode, with isotropic displacement parameters of 1.5 (H atoms of methyl groups) and 1.2 (all other H atoms) times U_{eq} of the parent atom. H atoms of oxy groups were refined freely with U_{iso} equal $1.5U_{eq}$ of corresponding O atom. In the absence of significant anomalous scattering effects, Friedel pairs have been merged. The absolute configuration can not be determined from the diffraction data, but is known from the synthesis and has been assumed in the refinement.

Data collection: *SMART* (Bruker, 1998–2000); cell refinement: *SAINT* (Bruker, 1998–2000); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *SHELXTL* (Bruker, 1998–2000); software used to prepare material for publication: *SHELXTL*.

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