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An intermediate in a new synthesis approach to β-substituted β-hydroxyaspartame

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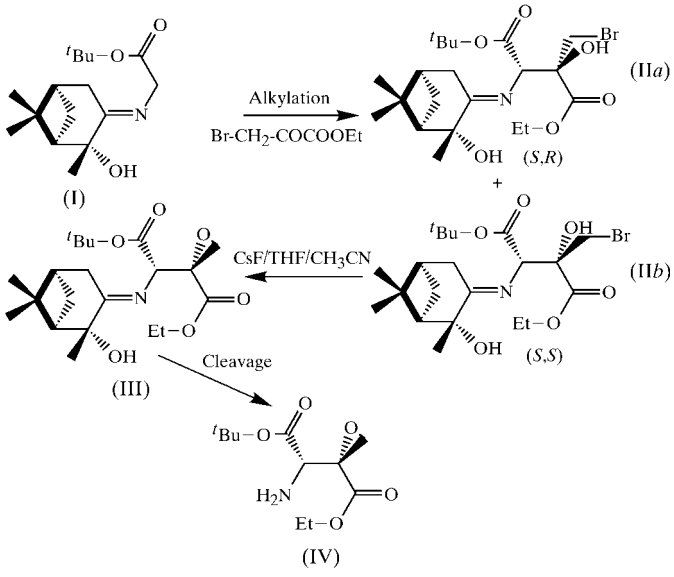
The crystal and molecular structure of 1-*tert*-butyl 4-ethyl (2′*R*,3′*R*,5′*R*,2*S*,3*S*)-3-bromomethyl-3-hydroxy-2-[(2′-hydroxy-2′,6′,6′-trimethylbicyclo[3.1.1]hept-3′-ylidene)amino]succinate, $C_{21}H_{34}BrNO_6$, is presented. This compound is an intermediate in the new synthetic route to β-substituted β-hydroxyaspartates, which are blockers of glutamate transport.

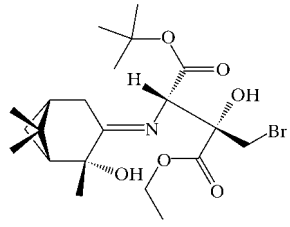
Comment

L-Glutamate is the major exitatory neurotransmitter in the mammalian central nervous system. The glutamate uptake system consists of at least five different transporter proteins called excitatory amino acid transporters, EAAT1–EAAT5,



which have been cloned from mammalian tissues. It has been reported that among investigated derivatives of DL-*threo*-β-hydoxyaspartate, L-*threo*-β-benzyloxyaspartate (L-TBOA) was the most potent blocker for human EAAT3, while the D-isomer revealed a difference in the pharmacophores between EAAT1 and EAAT3. Synthesis of various analogues of β-hydroxyaspartate, and especially of β-substituted β-hydroxyaspartates, will provide indispensable tools for the investigation of the physiological roles of glutamate transporters (Wehbe *et al.*, 2003). For the synthesis of β-substituted β-hydroxy-α-amino acids, and in particular of β-hydroxyaspartates (Lebrun *et al.*, 1997; Shimamoto *et al.*, 1998), we have explored a new strategy using the enolate, (I), of the Schiff base prepared from (+)-(1*R*,2*R*,5*R*)-2-hydroxypinan-3-one and *tert*-butyl glycinate (El Achkar *et al.*, 1988). This strategy is outlined in the reaction *Scheme* above.

The products are the epoxides (III) and (IV), which are versatile intermediates in organic chemistry (Hauser & Ellenberger, 1986) and would be good precursors for the synthesis of diversely β-substituted β-hydroxyaspartates and their derivatives. In order to determine unambiguously the configuration of the different asymmetric C atoms at different synthesis steps, the structure of the key intermediate (II*b*) was studied by X-ray diffraction.



(II*b*)

Fig. 1 shows the molecular structure of (II*b*), and selected geometric parameters are given in Table 1. Taking into account the known *R* configurations of atoms C2′, C3′ and C5′, we found that atoms C2 and C3 exhibit an *S* configuration. The bicyclic system from (+)-(1*R*,2*R*,5*R*)-2-hydroxypinan-3-one consists of a six-membered ring (C1′–C6′), bridged between atoms C3′ and C5′, with two methyl groups attached to atom C8′, and a methyl and a hydroxyl group attached to atom C2′. The N atom of the future amine function is involved in a Schiff base with an *E* configuration at the C1′=N1 bond. This *E* configuration was also found in the X-ray structure of several similar Schiff bases (Laue *et al.*, 2000; Thieme *et al.*, 2000; Katagiri *et al.*, 2001). As shown by the C2—N1—C1′—C2′ and C2—N1—C1′—C6′ torsion angles [175.9 (3) and −0.1 (5)°, respectively], the geometry of the double bond is slightly distorted.

The packing, shown in Fig. 2, is characterized by inter- and intramolecular hydrogen bonds (Table 2). Atom O3 in the reference molecule acts as a hydrogen-bond donor, *via* atom H3, to atoms O4′ and O2′^{i} [symmetry code: (i) $-x, y-\frac{1}{2}, -z$]. In addition, atom O2′ acts as a hydrogen-bond donor, *via* atom H2′, to atom N1. The two short intramolecular hydrogen bonds [O3···O4′ = 2.729 (4) Å and O2′···N1 = 2.877 (4) Å] hold the molecule in a rigid conformation by forming two five-membered rings. The intermolecular O3—H3···O2′^{i} hydrogen bond [O···O = 2.768 (4) Å], and propagation of this bond

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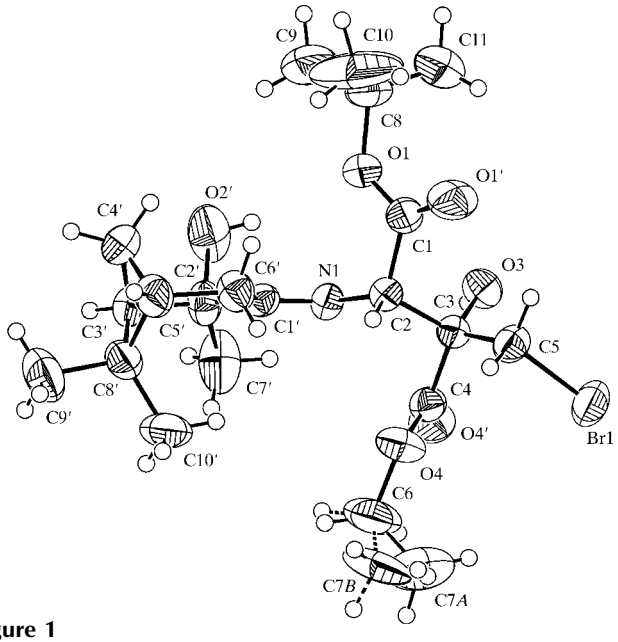

Figure 1
An *ORTEP*II (Johnson, 1976) view of the molecular structure of (II*b*), showing the labelling of all non-H atoms. Displacement ellipsoids are shown at the 50% probability level and H atoms are shown as circles of arbitrary radii.

from the molecule at $(-x, y-\frac{1}{2}, -z)$ to the molecule at $(x, y-1, z)$, generates an infinite chain running parallel to the [010] direction.

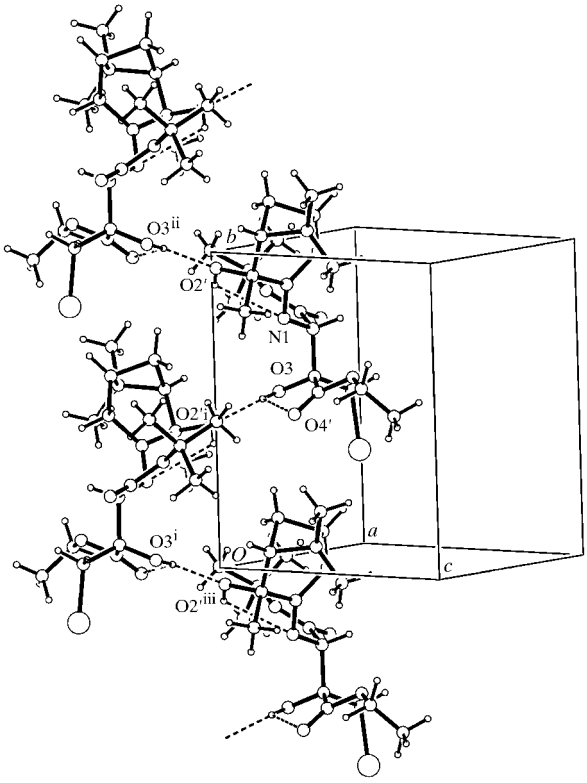

Figure 2
A *PLATON* (Spek, 2003) view of the intra- and intermolecular hydrogen-bonded motif of (II*b*). Only atoms involved in hydrogen bonding are labelled. C, O, N and H atoms are shown as spheres of arbitrary radii and hydrogen bonds are shown as dashed lines. [Symmetry codes: (i) $-x, y-\frac{1}{2}, -z$; (ii) $-x, y+\frac{1}{2}, -z$; (iii) $x, y-1, z$.]

Experimental

Potassium hexamethyldisilazane (KHMDS) gave the best result in preparing the potassium Schiff base enolate. Alkylation with ethyl bromopyruvate as prochiral ketone (Soloshonok *et al.*, 1997) afforded the β-hydroxy compounds (II*a*) and (II*b*) in 74% yield as a mixture of two diastereoisomers (88/12), which were separated by silica-gel column chromatography. For the X-ray diffraction analysis, pure (II*b*) (m.p. 365–366 K) was dissolved in the required amount of anhydrous Et_2O. Single crystals were grown from the solution by slow evaporation at room temperature. Compound (II*b*) was transformed easily into epoxide (III) by the action of CsF in tetrahydrofuran/CH_3CN (1/1) (yield 76%). After cleavage of the chiral auxiliary group, the aminoester epoxide (IV) was obtained (yield 50%).

Crystal data

$C_{21}H_{34}BrNO_6$	$D_x = 1.297$ Mg m^{-3}
$M_r = 476.39$	Mo $K\alpha$ radiation
Monoclinic, $P2_1$	Cell parameters from 24 309 reflections
$a = 11.546$ (2) Å	$\theta = 3.5$–$28.6°$
$b = 10.321$ (3) Å	$\mu = 1.72$ mm^{-1}
$c = 11.594$ (4) Å	$T = 293$ (2) K
$\beta = 118.031$ (5)°	Prism, colourless
$V = 1219.6$ (6) Å^3	0.50 × 0.40 × 0.20 mm
$Z = 2$	

Data collection

Nonius KappaCCD area-detector diffractometer	3231 independent reflections
	2981 reflections with $I > 2\sigma(I)$
φ scans	$R_{int} = 0.046$
Absorption correction: multi-scan (*SORTAV*; Blessing, 1995)	$\theta_{max} = 28.6°$
	$h = -15 \rightarrow 14$
$T_{min} = 0.487$, $T_{max} = 0.709$	$k = -13 \rightarrow 13$
24 309 measured reflections	$l = -14 \rightarrow 15$

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0432P)^2 + 0.5864P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)] = 0.046$	
$wR(F^2) = 0.119$	$(\Delta/\sigma)_{max} < 0.001$
$S = 1.05$	$\Delta\rho_{max} = 0.71$ e Å^{-3}
2981 reflections	$\Delta\rho_{min} = -0.57$ e Å^{-3}
281 parameters	
H-atom parameters constrained	

Table 1
Selected geometric parameters (Å, °).

C7*A*—C6—O4	116.6 (11)	C7*B*—C6—O4	108.6 (7)
C1—C2—C3—O3	−47.5 (3)	C1—C2—C3—C4	−168.1 (2)
N1—C2—C3—C5	−165.5 (2)	C2—C3—C5—Br1	171.37 (19)
C1—C2—C3—C5	72.1 (3)	C4—O4—C6—C7*A*	148.5 (14)
N1—C2—C3—C4	−45.8 (3)	C4—O4—C6—C7*B*	107.9 (8)

Table 2
Hydrogen-bonding geometry (Å, °).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O3—H3···O4′	0.82	2.31	2.729 (4)	113
O2′—H2′···N1	0.82	2.51	2.877 (4)	108
O3—H3···O2′i	0.82	2.00	2.768 (4)	156

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

Atoms H3 and H2′, which are involved in hydrogen bonds, were located in difference Fourier maps. The remaining H atoms were introduced at calculated positions and refined as riding atoms (O—H = 0.82 Å, and C—H = 0.96, 0.97 and 0.98 Å), with displacement parameters equal to 1.2 (OH, CH and CH_2) or 1.5 (CH_3) times that of the parent atom. It was clear early in the refinement that there was some disorder of the methyl atom C7 of the ethyl ester function. The ethyl ester group was therefore refined as a disordered group with an occupancy of 35% for the C7*A* position and 67% for the C7*B* position. Although atom C10 of the *tert*-butyl group displays an elongated ellipsoid axis, no chemically sensible disordered model could be obtained. This is due to its close interactions with two methyl groups, *viz*. methyl atom C7*A* of a symmetry-related molecule at $(1-x, y+\frac{1}{2}, 1-z)$ and methyl atom C11 of a symmetry-related molecule at $(1-x, y+\frac{1}{2}, -z)$. As discussed above, the absolute configuration of atoms C2, C3 and C5 was established from the known absolute configuration of atoms C2′, C3′ and C5′; it was therefore not imperative to determine the configuration from the anomalous dispersion of the Br atom, and no Friedel pairs were collected.

Data collection: *KappaCCD Software* (Nonius, 1997); cell refinement: *HKL SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *HKL DENZO* (Otwinowski & Minor, 1997) and *SCALEPACK*; program(s) used to solve structure: *SIR*97 (Altomare *et al.*, 1998); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*II (Johnson, 1976), *PLATON* (Spek, 2003); software used to prepare material for publication: *maXus* (Mackay *et al.*, 1999).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: DN1023). Services for accessing these data are described at the back of the journal.

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