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Two key chiral intermediates in a new 4-hydroxyisoleucine synthesis

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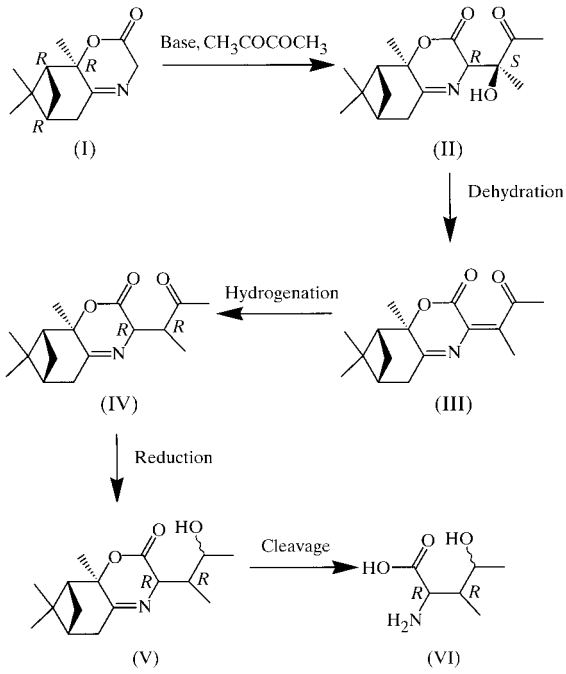
We present the crystal and molecular structure of two key compounds of a new synthesis strategy for isomers of natural (2*S*,3*R*,4*S*)-4-hydroxyisoleucines, 2,3,5,6,7,8-hexahydro-3-(1-hydroxy-1-methyl-2-oxopropyl)-6,8-methano-7,7,8a-trimethyl-5*H*-1,4-benzoxazin-2-one, $C_{16}H_{23}NO_4$, and 2,3,5,6,7,8-hexahydro-3-(1-methyl-2-oxopropyl)-6,8-methano-7,7,8a-trimethyl-5*H*-1,4-benzoxazin-2-one, $C_{16}H_{23}NO_3$. A new optically pure chiral oxazinone auxiliary derived from (1*R*,2*R*,5*R*)-2-hydroxypinan-3-one was used.

Comment

As part of an ongoing study aimed at synthesizing γ-hydroxy α-aminoacids (Jacob *et al.*, 1997) and in particular 4-hydroxyisoleucine, we explored a new strategy using as a starting material the oxazinone (El Achkar *et al.*, 1988) derived from (1*R*,2*R*,5*R*)-2-hydroxypinan-3-one. The natural isomer (2*S*,3*R*,4*S*)-4-hydroxyisoleucine extracted from fenugreek seeds known in traditional medicine for its antidiabetic properties was recently characterized as a new insulinotropic compound (Sauvaire *et al.*, 1998). For structure–activity studies it was necessary to prepare enantiomerically pure isomers of 4-hydroxyisoleucine and their precursors (Kassem *et al.*, 2000). To know unambiguously the configuration of the different asymmetric C atoms at different synthesis steps, the structures of two key intermediates, (II) and (IV), were studied by X-ray diffraction. From the known *R* configuration of C7, C10 and C12 we found the *R* configuration for C2 and the *S* for C3 in compound (II), and the *R* configuration for C2 and C3 in compound (IV). The procedure used is outlined in the reaction scheme below.

Compounds (II) and (IV) have similar structures except the O3 hydroxyl group attached to the C3 atom in (II) is replaced by an H atom in compound (IV). They are composed of the six-membered ring (C1, C2, N1, C8, C7, O1) of the oxazinone sharing one side (C7—C8) with the bicyclo system from the (1*R*,2*R*,5*R*)-2-hydroxypinan-3-one and on C2 the future amino-acid side chain (C3—C4—C5). The C1, C2, N1, C8, C7, O1 ring can be described as having a boat conformation with greater distortion for compound (IV) than for (II). The atoms



C2 and C7 are, respectively, 0.387 (6) and 0.507 (5) Å above the mean plane of the other four atoms (r.m.s. $\Delta = 0.090$ Å) for compound (II). However, for compound (IV), C2 and C7 are, respectively, 0.526 (6) and 0.517 (6) Å out of the same mean

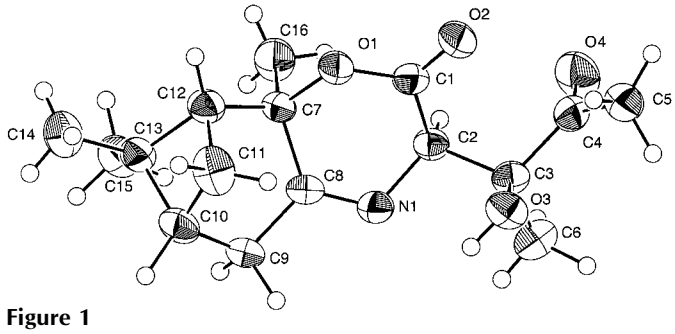


Figure 1
An *ORTEP*II (Johnson, 1976) view of the molecular structure of (II) showing the labelling of all non-H atoms. Displacement ellipsoids are shown at the 50% probability level and H atoms are drawn as circles of arbitrary radius.

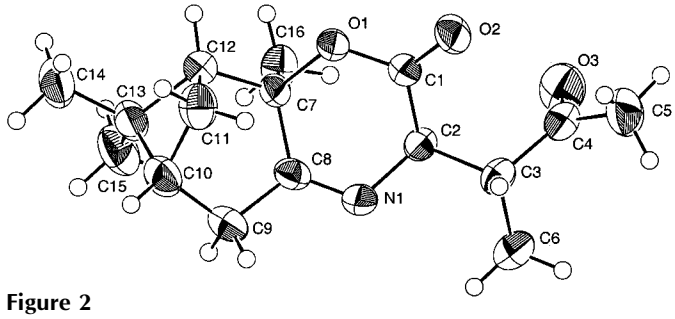


Figure 2
An *ORTEP*II (Johnson, 1976) view of the molecular structure of (IV) showing the labelling of all non-H atoms. Displacement ellipsoids are shown at the 50% probability level and H atoms are drawn as circles of arbitrary radius.

plane (r.m.s. $\Delta = 0.099$ Å). This is also indicated by the torsion angles O1—C1—C2—N1 of 29.2 (1) and 43.0 (1)°, respectively. The bicyclo system consists of a six-membered ring (C7, C8, C9, C10, C11, C12) bridged between C12 and C10 with C13. Three methyl groups are attached to this bicyclo system, two at C13 and one at C7.

Experimental

The enantioselective condensation of butan-2,3-dione on (I) resulted in alcohol (II). After a dehydration step, stereoselective hydrogenation of the double bond of (III) gave the second optically pure intermediate, (IV). After reduction, the final cleavage of the chiral auxiliary produced two pure isomers of 4-hydroxyisoleucine. Pure (II) (m.p. 375–377 K) and (IV) (m.p. 382–384 K) were dissolved in anhydrous Et_2O and the solutions evaporated slowly at room temperature to produce crystals.

Compound (II)

Crystal data

$C_{16}H_{23}NO_4$
$M_r = 293.363$
Orthorhombic, $P2_12_12_1$
$a = 11.0434$ (5) Å
$b = 11.0028$ (3) Å
$c = 12.7460$ (6) Å
$V = 1548.70$ (10) Å^3
$Z = 4$
$D_x = 1.258$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 9594 reflections
$\theta = 1.00$–$26.24°$
$\mu = 0.09$ mm^{-1}
$T = 298$ K
Prism, colourless
0.40 × 0.30 × 0.20 mm

Data collection

KappaCCD area-detector diffractometer
φ scans
9422 measured reflections
1719 independent reflections
1576 reflections with $I > 3\sigma(I)$
$R_{int} = 0.062$
$\theta_{max} = 26.24°$
$h = -13 \rightarrow 13$
$k = -12 \rightarrow 12$
$l = -14 \rightarrow 15$

Refinement

$R = 0.041$
$wR = 0.058$
$S = 1.319$
1576 reflections
190 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + 0.03F_o^2]$
$(\Delta/\sigma)_{max} = 0.005$
$\Delta\rho_{max} = 0.14$ e Å^{-3}
$\Delta\rho_{min} = -0.16$ e Å^{-3}

Table 1
Selected geometric parameters (Å, °) for (II).

O1—C1	1.3427 (6)	C1—C2	1.5158 (7)
O1—C7	1.4691 (6)	C2—C3	1.5370 (7)
O2—C1	1.2028 (6)	C3—C4	1.5273 (7)
O3—C3	1.4332 (6)	C3—C6	1.5168 (8)
O4—C4	1.2141 (6)	C4—C5	1.4952 (8)
N1—C2	1.4546 (6)	C7—C8	1.5106 (7)
N1—C8	1.2716 (6)		
C1—O1—C7	119.1 (1)	O3—C3—C4	109.2 (1)
C2—N1—C8	117.4 (1)	O3—C3—C6	109.0 (1)
O1—C1—O2	119.0 (1)	C2—C3—C4	109.8 (1)
O1—C1—C2	116.7 (1)	C2—C3—C6	111.9 (1)
O2—C1—C2	124.3 (1)	C4—C3—C6	108.1 (1)
N1—C2—C1	113.5 (1)	O4—C4—C3	117.5 (1)
N1—C2—C3	108.2 (1)	O4—C4—C5	122.4 (1)
C1—C2—C3	110.1 (1)	C3—C4—C5	120.0 (1)
O3—C3—C2	108.7 (1)	O1—C7—C8	107.5 (1)
O1—C1—C2—C3	−150.7 (1)	C2—C3—C4—C5	129.0 (1)
C1—C2—C3—C4	−56.7 (1)		

Compound (IV)

Crystal data

$C_{16}H_{23}NO_3$
$M_r = 277.364$
Orthorhombic, $P2_12_12_1$
$a = 8.2610$ (3) Å
$b = 12.5168$ (5) Å
$c = 14.9291$ (3) Å
$V = 1543.69$ (9) Å^3
$Z = 4$
$D_x = 1.193$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 11 140 reflections
$\theta = 1.00$–$26.37°$
$\mu = 0.082$ mm^{-1}
$T = 298$ K
Prism, colourless
0.40 × 0.30 × 0.20 mm

Data collection

KappaCCD area-detector diffractometer
φ scans
10 011 measured reflections
1793 independent reflections
1630 reflections with $I > 3\sigma(I)$
$R_{int} = 0.028$
$\theta_{max} = 26.37°$
$h = -10 \rightarrow 10$
$k = -14 \rightarrow 15$
$l = -18 \rightarrow 18$

Refinement

$R = 0.039$
$wR = 0.060$
$S = 1.309$
1630 reflections
181 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + 0.03F_o^2]$
$(\Delta/\sigma)_{max} = 0.001$
$\Delta\rho_{max} = 0.17$ e Å^{-3}
$\Delta\rho_{min} = -0.31$ e Å^{-3}

Table 2
Selected geometric parameters (Å, °) for (IV).

O1—C1	1.3412 (6)	C1—C2	1.5138 (7)
O1—C7	1.4772 (6)	C2—C3	1.5228 (7)
O2—C1	1.2059 (6)	C3—C4	1.5124 (8)
O3—C4	1.2108 (7)	C3—C6	1.5235 (9)
N1—C2	1.4736 (7)	C4—C5	1.4867 (9)
N1—C8	1.2687 (6)	C7—C8	1.5266 (8)
C1—O1—C7	118.6 (1)	C2—C3—C4	111.2 (1)
C2—N1—C8	115.9 (1)	C2—C3—C6	110.9 (1)
O1—C1—O2	119.5 (1)	C4—C3—C6	107.3 (1)
O1—C1—C2	116.6 (1)	O3—C4—C3	120.4 (1)
O2—C1—C2	123.8 (1)	O3—C4—C5	122.0 (1)
N1—C2—C1	109.6 (1)	C3—C4—C5	117.5 (1)
N1—C2—C3	110.4 (1)	O1—C7—C8	106.1 (1)
C1—C2—C3	111.3 (1)		
O1—C1—C2—C3	−165.4 (1)	C6—C3—C4—O3	77.0 (1)
C1—C2—C3—C4	−59.8 (1)		

For both structures, the H atoms were introduced at calculated positions and refined as riding with an isotropic displacement parameter $U(H)_{eq} = U_{eq} + 0.02$ of the parent atoms [parent + option of *maXus* (Mackay *et al.*, 1999)].

For both compounds, data collection: *KappaCCD* (Nonius, 1998); data reduction: *DENZO* and *SCALEPAK* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SIR*92 (Altomare *et al.*, 1994); program(s) used to refine structure: *maXus* (Mackay *et al.*, 1999); molecular graphics: *ORTEP*II (Johnson, 1976); software used to prepare material for publication: *maXus*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GS1091). Services for accessing these data are described at the back of the journal.

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