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Full stereochemical understanding in a new (2*R*,3*R*,4*R*)-4-hydroxyisoleucine synthesis

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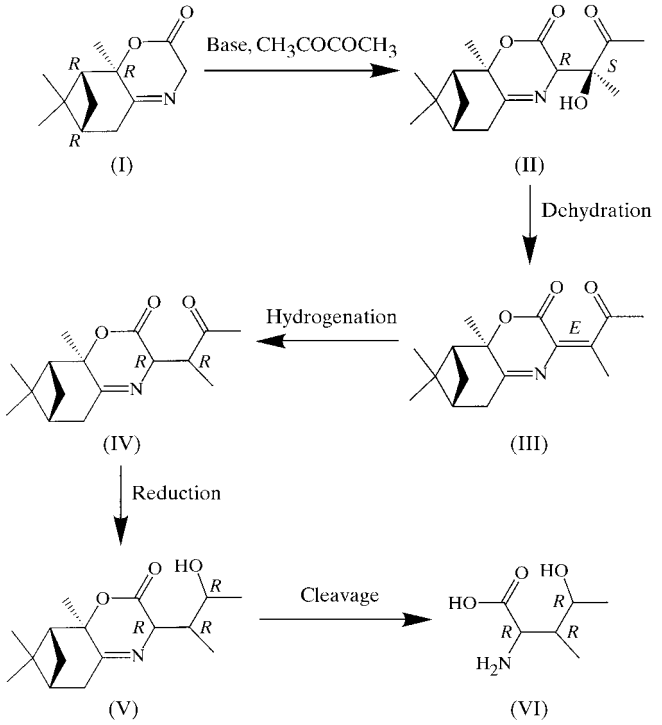
We present the crystal and molecular structures of 2,3,6,7,8,8a-hexahydro-6,8-methano-7,7,8a-trimethyl-3-(1-methyl-2-oxopropylidene)-5*H*-1,4-benzoxazin-2-one, $C_{16}H_{21}NO_3$, (III), and 2,3,6,7,8,8a-hexahydro-3-(2-hydroxy-1-methylpropyl)-6,8-methano-7,7,8a-trimethyl-5*H*-1,4-benzoxazin-2-one, $C_{16}H_{25}NO_3$, (V). These compounds are two of the four key intermediates in our synthetic route to (2*R*,3*R*,4*R*)-4-hydroxyisoleucine. The two structures provide a full understanding of the stereochemistry in successive steps. This synthesis was based on a new optically pure chiral oxazinone auxiliary derived from (1*R*,2*R*,5*R*)-2-hydroxypinan-3-one.

Comment

For the synthesis of γ-hydroxy-α-amino acids (Jacob *et al.*, 1997), and in particular 4-hydroxyisoleucine, we have explored a new strategy using the oxazinone (El Achkar *et al.*, 1988) derived from (1*R*,2*R*,5*R*)-2-hydroxypinan-3-one as the starting material. By this route, enantiomerically pure isomers of (2*R*,3*R*,4*R*)-4-hydroxyisoleucine have been prepared (Kassem *et al.*, 2001). The strategy used is outlined in the reaction Scheme below. We have recently described the molecular structures of compounds (II) and (IV) (Kassem *et al.*, 2000). At that time, we did not possess crystals of compounds (III) and (V) of sufficient quality to be able to determine their structure and stereochemistry, and without this information it is difficult to obtain a full stereochemical understanding of the different steps in the synthetic route; a particular requirement is the structure of the key didehydro intermediate, (III).

During the enantioselective synthesis of 4-hydroxyisoleucine from the oxazinone, (I), three stereogenic centres were created, the key intermediate being the chiral didehydro amino acid derivative, (III), where hydrogenation of the double bond would allow control of the configurations of atoms C2 and C3. The configuration of atom C3 controls the stereochemistry of atom C4 after reduction of the ketone. Hence, it is necessary to determine the geometry of the double bond of (III) and the configuration of atom C4 in compound (IV).



For these intermediates, we found the *R* configuration for C2 and *S* for C3 in compound (II), and the *R* configuration for both C2 and C3 in compound (IV). To determine the stereochemistry unambiguously during the dehydration step from (II) to (III), and the reduction step between (IV) and (V), the structures of two key intermediates, (III) and (V), were determined, and their structures are presented here.

The C2═C3 double bond was found to have the *E* configuration in compound (III). From the known *R* configuration of C7, C10 and C12, corresponding to the chiral auxiliary oxazinone, we found the *R* configuration for C2, C3 and C4 in compound (V).

Compounds (III) and (V) have different structures. The carbonyl group on C4 and the C2═C3 double bond in compound (III) were reduced in two steps, producing three asymmetric C atoms, *viz.* C2, C3 and C4, in compound (V).

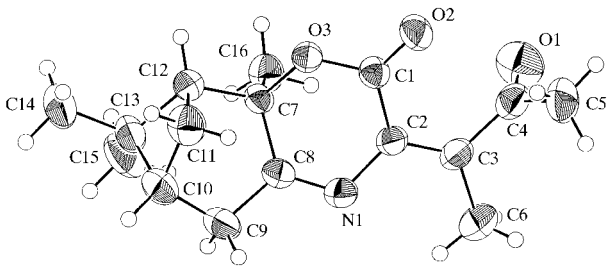


Figure 1
A view of the molecular structure of (III) showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

The six-membered C1—C2—N1—C8—C7—O3 ring of the oxazinone shares one side (C7—C8) with the bicyclo system of the (1*R*,2*R*,5*R*)-2-hydroxypinan-3-one. On atom C2 is found the future amino acid side chain (C3—C4—C5).

The C1—C2—N1—C8—C7—O3 ring can be described as having a boat conformation, with slight distortion differences between (III) and (V). Atoms C2 and C7 are 0.2915 (17) and 0.5533 (17) Å, respectively, above the mean plane of the other four atoms (r.m.s. deviation = 0.065 Å) in (III). However, in (V), atoms C2 and C7 are 0.3347 (17) and 0.5163 (18) Å, respectively, out of the same mean plane (r.m.s. deviation = 0.066 Å). This difference is better indicated by the C8—N1—C2—C3 torsion angle, which is −158.28 (19)° in (III) and 155.44 (17)° in (V). In compound (III), a partial conjugation of the C2═C3 double bond with C8═N1 can be observed, but not with the carbonyl group of the ketone.

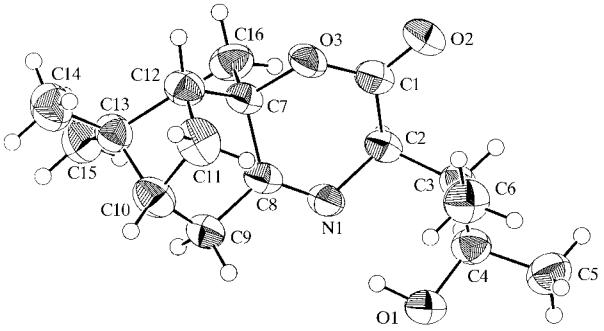


Figure 2
A view of the molecular structure of (V) showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

The bicyclo system, including the six-membered C7—C8—C9—C10—C11—C12 ring, is bridged by atom C13 between C12 and C10.

Experimental

The enantioselective condensation of butane-2,3-dione with (1′*R*,2′*R*,5′*R*)-oxazinone (I) resulted in alcohol (II). After a dehydration step, a stereoselective hydrogenation of the double bond of compound (III) gave the second optically pure intermediate, (IV). After a reduction step, the final cleavage of the chiral auxiliary produced one pure isomer of 4-hydroxyisoleucine. Crystals of (III) (m.p. 375–377 K) and (V) (m.p. 382–384 K) suitable for single-crystal X-ray diffraction were grown from solutions in diethyl ether.

Compound (III)

Crystal data

$C_{16}H_{21}NO_3$
M_r = 275.34
Orthorhombic, $P2_12_12_1$
a = 8.4160 (3) Å
b = 12.3127 (5) Å
c = 14.7039 (4) Å
V = 1523.72 (9) Å^3
Z = 4
D_x = 1.200 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 10 878 reflections
θ = 1.0–26.4°
μ = 0.08 mm^{-1}
T = 293 (2) K
Prism, colourless
0.4 × 0.3 × 0.2 mm

Data collection

Nonius KappaCCD area-detector diffractometer
φ scans
10 878 measured reflections
1775 independent reflections
1668 reflections with $I > 2\sigma(I)$
R_{int} = 0.033
θ_{max} = 26.4°
$h = -10 \rightarrow 10$
$k = -15 \rightarrow 15$
$l = -17 \rightarrow 17$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.038
$wR(F^2)$ = 0.100
S = 1.06
1775 reflections
181 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0551P)^2 + 0.1091P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.13 e Å^{-3}
$\Delta\rho_{min}$ = −0.16 e Å^{-3}

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

O1—C4	1.205 (3)	C1—C2	1.488 (2)
O2—C1	1.207 (2)	C2—C3	1.342 (3)
O3—C1	1.340 (2)	C3—C4	1.495 (3)
O3—C7	1.476 (2)	C3—C6	1.499 (3)
N1—C8	1.277 (2)	C4—C5	1.493 (3)
N1—C2	1.407 (2)	C7—C8	1.524 (3)
C1—O3—C7	117.87 (12)	C2—C3—C4	122.92 (17)
C8—N1—C2	117.02 (15)	C2—C3—C6	123.1 (2)
O2—C1—O3	119.63 (15)	C4—C3—C6	113.88 (19)
O2—C1—C2	123.97 (17)	O1—C4—C5	122.3 (2)
O3—C1—C2	116.31 (15)	O1—C4—C3	120.2 (2)
C3—C2—N1	121.62 (17)	C5—C4—C3	117.2 (2)
C3—C2—C1	120.13 (17)	O3—C7—C8	106.86 (14)
N1—C2—C1	117.79 (16)	N1—C8—C7	121.67 (16)
C8—N1—C2—C3	−158.28 (19)	C2—C3—C4—O1	−85.9 (3)
O3—C1—C2—C3	164.23 (18)	C2—C3—C4—C5	99.3 (3)
C1—C2—C3—C4	−5.4 (3)		

Compound (V)

Crystal data

$C_{16}H_{25}NO_3$
M_r = 279.37
Orthorhombic, $P2_12_12_1$
a = 10.2905 (3) Å
b = 11.8864 (5) Å
c = 12.8317 (5) Å
V = 1569.50 (10) Å^3
Z = 4
D_x = 1.182 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 11 088 reflections
θ = 1.0–26.3°
μ = 0.08 mm^{-1}
T = 293 (2) K
Prism, colourless
0.4 × 0.3 × 0.2 mm

Data collection

Nonius KappaCCD area-detector diffractometer
φ scans
11 088 measured reflections
1791 independent reflections
1638 reflections with $I > 2\sigma(I)$
R_{int} = 0.036
θ_{max} = 26.3°
$h = -12 \rightarrow 12$
$k = -14 \rightarrow 14$
$l = -16 \rightarrow 16$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.038
$wR(F^2)$ = 0.100
S = 1.06
1791 reflections
181 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0677P)^2 + 0.1278P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.13 e Å^{-3}
$\Delta\rho_{min}$ = −0.12 e Å^{-3}

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

O1—C4	1.427 (2)	C1—C2	1.519 (3)
O2—C1	1.200 (2)	C2—C3	1.545 (3)
O3—C1	1.346 (3)	C3—C6	1.521 (3)
O3—C7	1.474 (2)	C3—C4	1.533 (3)
N1—C8	1.262 (2)	C4—C5	1.515 (3)
N1—C2	1.468 (2)	C7—C8	1.525 (2)
C1—O3—C7	118.99 (15)	C6—C3—C4	112.55 (16)
C8—N1—C2	118.69 (16)	C6—C3—C2	111.30 (17)
O2—C1—O3	118.40 (18)	C4—C3—C2	111.10 (16)
O2—C1—C2	123.97 (19)	O1—C4—C5	106.75 (19)
O3—C1—C2	117.58 (16)	O1—C4—C3	112.48 (17)
N1—C2—C1	113.49 (16)	C5—C4—C3	112.8 (2)
N1—C2—C3	108.85 (14)	O3—C7—C8	107.15 (15)
C1—C2—C3	110.92 (16)	N1—C8—C7	122.67 (17)
C8—N1—C2—C3	155.42 (17)	C2—C3—C4—O1	−70.2 (2)
O3—C1—C2—C3	−145.74 (17)	C2—C3—C4—C5	168.94 (18)
C1—C2—C3—C4	−172.90 (15)		

For both structures, the H atoms were introduced at calculated positions and refined as riding (O—H = 0.82 Å, and C—H = 0.96, 0.97 or 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.

For both compounds, data collection: *KappaCCD Reference Manual* (Nonius, 1998); data reduction: *DENZO* and *SCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SIR*92 (Altomare *et al.*, 1994); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*II (Johnson, 1976); 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: GD1165). Services for accessing these data are described at the back of the journal.

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