



**HAL**  
open science

## Two key chiral intermediates in a new 4-hydroxyisoleucine synthesis

Tarek Kassem, Valérie Rolland, Jean Martinez, Marc Rolland

► **To cite this version:**

Tarek Kassem, Valérie Rolland, Jean Martinez, Marc Rolland. Two key chiral intermediates in a new 4-hydroxyisoleucine synthesis. *Acta Crystallographica Section C: Crystal Structure Communications* [1968-2013], 2000, 56 (8), pp.1037-1039. 10.1107/s010827010000740x . hal-04675787

**HAL Id: hal-04675787**

**<https://hal.science/hal-04675787v1>**

Submitted on 25 Aug 2024

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

## Two key chiral intermediates in a new 4-hydroxyisoleucine synthesis

Tarek Kassem, Valérie Rolland, Jean Martinez and Marc Rolland

Copyright © International Union of Crystallography

Author(s) of this paper may load this reprint on their own web site provided that this cover page is retained. Republication of this article or its storage in electronic databases or the like is not permitted without prior permission in writing from the IUCr.

## Two key chiral intermediates in a new 4-hydroxyisoleucine synthesis

Tarek Kassem, Valérie Rolland, Jean Martinez and Marc Rolland\*

Laboratoire des Aminoacides, Peptides et Protéines, Université Montpellier I et II, Faculté de Pharmacie, UMR CNRS 5810, 15 Avenue Charles Flahault, 34060 Montpellier CEDEX 2, France

Correspondence e-mail: rolland@colombes.pharma.univ-montp1.fr

Received 20 March 2000

Accepted 17 May 2000

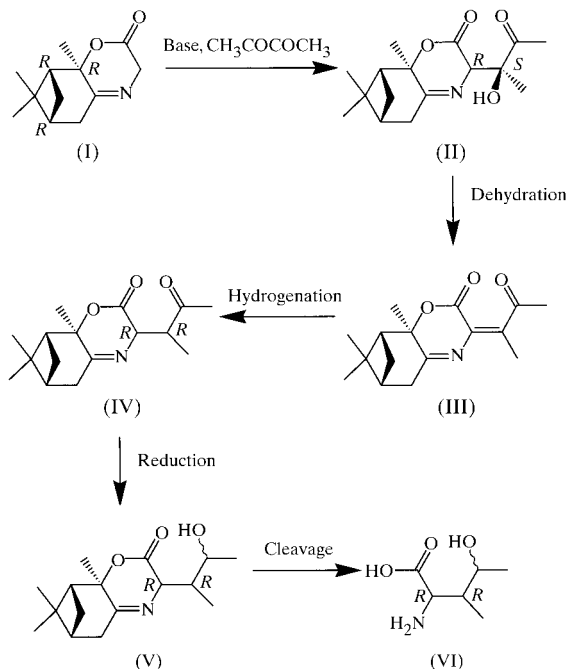
We present the crystal and molecular structure of two key compounds of a new synthesis strategy for isomers of natural (2*S*,3*R*,4*S*)-4-hydroxyisoleucines, 2,3,5,6,7,8-hexahydro-3-(1-hydroxy-1-methyl-2-oxopropyl)-6,8-methano-7,7,8a-trimethyl-5*H*-1,4-benzoxazin-2-one, C<sub>16</sub>H<sub>23</sub>NO<sub>4</sub>, 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<sub>16</sub>H<sub>23</sub>NO<sub>3</sub>. A new optically pure chiral oxazinone auxiliary derived from (1*R*,2*R*,5*R*)-2-hydroxypinan-3-one was used.

### Comment

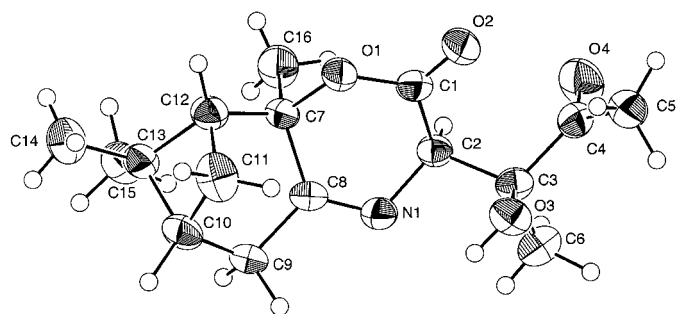
As part of an ongoing study aimed at synthesizing  $\gamma$ -hydroxy  $\alpha$ -aminoacids (Jacob *et al.*, 1997) and in particular 4-hydroxyisoleucine, we explored a new strategy using as a starting material the oxazinone (El Achkar *et al.*, 1988) derived from (1*R*,2*R*,5*R*)-2-hydroxypinan-3-one. 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,

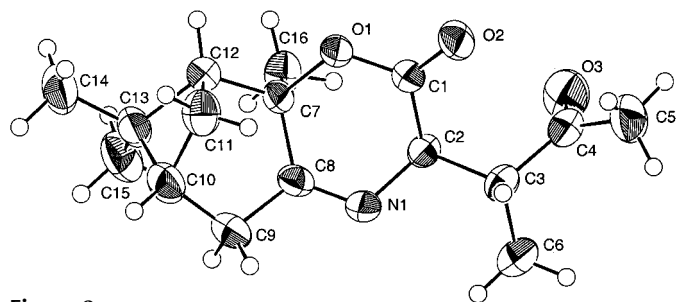
O1 ring can be described as having a boat conformation with greater distortion for compound (IV) than for (II). The atoms



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 (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 (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.  $\Delta = 0.099 \text{ \AA}$ ). 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<sub>2</sub>O and the solutions evaporated slowly at room temperature to produce crystals.

### Compound (II)

#### Crystal data

C<sub>16</sub>H<sub>23</sub>NO<sub>4</sub>  
*M<sub>r</sub>* = 293.363  
 Orthorhombic, *P*<sub>2</sub><sup>1</sup><sub>2</sub><sup>1</sup><sub>2</sub><sup>1</sup>  
*a* = 11.0434 (5) Å  
*b* = 11.0028 (3) Å  
*c* = 12.7460 (6) Å  
*V* = 1548.70 (10) Å<sup>3</sup>  
*Z* = 4  
*D<sub>x</sub>* = 1.258 Mg m<sup>-3</sup>

Mo *K*α radiation  
 Cell parameters from 9594 reflections  
 $\theta = 1.00\text{--}26.24^\circ$   
 $\mu = 0.09 \text{ mm}^{-1}$   
*T* = 298 K  
 Prism, colourless  
 0.40 × 0.30 × 0.20 mm

#### Data collection

KappaCCD area-detector diffractometer  
 $\varphi$  scans  
 9422 measured reflections  
 1719 independent reflections  
 1576 reflections with *I* > 3σ(*I*)

*R*<sub>int</sub> = 0.062  
 $\theta_{\text{max}} = 26.24^\circ$   
*h* = -13 → 13  
*k* = -12 → 12  
*l* = -14 → 15

#### Refinement

*R* = 0.041  
*wR* = 0.058  
*S* = 1.319  
 1576 reflections  
 190 parameters

H-atom parameters constrained  
 $w = 1/[\sigma^2(F_o^2) + 0.03F_o^2]$   
 $(\Delta/\sigma)_{\text{max}} = 0.005$   
 $\Delta\rho_{\text{max}} = 0.14 \text{ e \AA}^{-3}$   
 $\Delta\rho_{\text{min}} = -0.16 \text{ e \AA}^{-3}$

**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<sub>16</sub>H<sub>23</sub>NO<sub>3</sub>  
*M<sub>r</sub>* = 277.364  
 Orthorhombic, *P*<sub>2</sub><sup>1</sup><sub>2</sub><sup>1</sup><sub>2</sub><sup>1</sup>  
*a* = 8.2610 (3) Å  
*b* = 12.5168 (5) Å  
*c* = 14.9291 (3) Å  
*V* = 1543.69 (9) Å<sup>3</sup>  
*Z* = 4  
*D<sub>x</sub>* = 1.193 Mg m<sup>-3</sup>

Mo *K*α radiation  
 Cell parameters from 11 140 reflections  
 $\theta = 1.00\text{--}26.37^\circ$   
 $\mu = 0.082 \text{ mm}^{-1}$   
*T* = 298 K  
 Prism, colourless  
 0.40 × 0.30 × 0.20 mm

#### Data collection

KappaCCD area-detector diffractometer  
 $\varphi$  scans  
 10 011 measured reflections  
 1793 independent reflections  
 1630 reflections with *I* > 3σ(*I*)

*R*<sub>int</sub> = 0.028  
 $\theta_{\text{max}} = 26.37^\circ$   
*h* = -10 → 10  
*k* = -14 → 15  
*l* = -18 → 18

#### Refinement

*R* = 0.039  
*wR* = 0.060  
*S* = 1.309  
 1630 reflections  
 181 parameters

H-atom parameters constrained  
 $w = 1/[\sigma^2(F_o^2) + 0.03F_o^2]$   
 $(\Delta/\sigma)_{\text{max}} = 0.001$   
 $\Delta\rho_{\text{max}} = 0.17 \text{ e \AA}^{-3}$   
 $\Delta\rho_{\text{min}} = -0.31 \text{ e \AA}^{-3}$

**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  $U(\text{H})_{\text{eq}} = U_{\text{eq}} + 0.02$  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: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *maXus* (Mackay *et al.*, 1999); molecular graphics: *ORTEPII* (Johnson, 1976); software used to prepare material for publication: *maXus*.

We thank Professor M. Pierrot and M. Giorgi, Laboratoire de Bio-inorganique Structurale (UMR CNRS 6517), Faculté des Sciences de St. Jérôme, Marseille, France, for data collection and kind help on the use of *maXus*.

---

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.

---

## References

- Altomare, A., Cascarano, G., Giacovazzo, C., Guagliardi, A., Burla, M. C., Polidori, G. & Camalli, M. (1994). *J. Appl. Cryst.* **27**, 435.
- El Achkar, A., Boumzebra, M., Roumestant, M. L. & Viallefont, P. (1988). *Tetrahedron*, **44**, 5319–5332.
- Jacob, M., Roumestant, M. L., Viallefont, P. & Martinez, J. (1997). *Synlett*. pp. 691–692.
- Johnson, C. K. (1976). *ORTEP*. Report ORNL-5138. Oak Ridge National Laboratory, Oak Ridge, Tennessee, USA.
- Kassem, T., Rolland, V., Rolland, M., Roumestant, M. L. & Martinez, J. (2000). *Tetrahedron*. In preparation.
- Mackay, S., Gilmore, C. J., Edwards, C., Stewart, N. & Shankland, K. (1999). *maXus*. Nonius, The Netherlands, MacScience, Japan and The University of Glasgow, Scotland.
- Nonius (1998). *KappaCCD Reference Manual*. Nonius BV, Delft, The Netherlands.
- Otwinowski, Z. & Minor, W. (1997). *Methods Enzymol.* **276**, 307–326.
- Sauvaire, Y., Petit, P., Broca, C., Manteghetti, M., Baissac, Y., Fernandez Alvarez, J., Gross, R., Roge, M., Leconte, A., Gomes, R. & Ribes, G. (1998). *Diabetes*, **17**, 206–210.