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(+)-(3*R*)-*N*-Hydroxy-2-[(*S*)-ethoxy(4-methoxyphenyl)-phosphoryl]-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

Kiriko Kurokawa,[a] Nobuko Kanehisa,[b]* Masaaki Sawa,[a] Hirosato Kondo[a] and Yasushi Kai[b]

[a]Chemistry Group, R&D Laboratories, Research and Development Division, Nippon Organon KK, 1-5-90 Tomobuchi-cho, Miyakojima-ku, Osaka 534-0016, Japan, and [b]Department of Materials Chemistry, Graduate School of Engineering, Osaka University, Suita, Osaka 565-0871, Japan

Correspondence e-mail: kanehisa@ap.chem.eng.osaka-u.ac.jp

Key indicators

Single-crystal X-ray study
T = 294 K
Mean σ(C–C) = 0.004 Å
R factor = 0.041
wR factor = 0.102
Data-to-parameter ratio = 10.6

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

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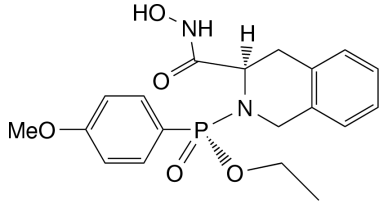
The title compound, $C_{19}H_{23}N_2O_5P$, is one of two diastereomers of an arylphosphonamide hydroxamate. The absolute configuration has been determined to establish the relationship between the stereochemistry at the P atom and the activity in inhibition of matrix metalloproteinases.

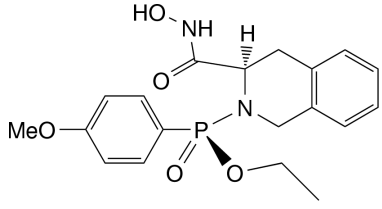
Comment

Matrix metalloproteinases (MMPs) are a family of zinc–metalloproteinases involved in the extracellular matrix degradation (Woessner, 1991). So far, more than 20 MMPs have been isolated and they are implicated in the pathological processes of a variety of diseases associated with excessive degradation of the extracellular matrix, such as tumor metastasis (Yip *et al.*, 1999), rheumatoid arthritis and osteoarthritis (Clark *et al.*, 2000), multiple sclerosis (Gijbels *et al.*, 1994). Therefore, a number of laboratories have vigorously conducted the development of MMP inhibitors as curatives of these diseases (Whittaker *et al.*, 1999).



inactive isomer (I)

Recently, our group has reported that a phosphonamide-based hydroxamate showed potent inhibitory activities against MMP-1, -3 and -9 (Sawa *et al.*, 2001). It was found that only one of the two diastereomers resulting from the chirality at the P atom showed potent inhibition against MMPs [active isomer: (II)], while the other isomer was inactive [inactive isomer: (I)]. This result suggested that the stereochemistry at the P atom was very important for the inhibition of the enzymes.

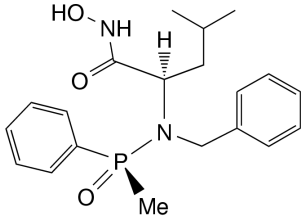


active isomer (II)

Therefore, the establishment of the absolute configuration of the P atom would be a great help in studying the interactions of the

inhibitor in the active sites of MMPs. Moreover, it seems to be worthwhile information for the design of protease inhibitors. The inactive isomer (I) was used for the X-ray analysis instead of the active isomer (II), because (I) could be much more easily crystallized than (II).

As shown in Fig. 1, the configuration of the P atom of the inactive isomer (I) was determined to be *S*. The configuration of one of the two chiral centers, the α-carbon of the hydroxamate group, was already known, because both (I) and (II) were synthesized from the known *R*-form of the starting material. The resultant configuration of the α-carbon, C2, is consistent with this stereochemistry (*R* configuration). Hence, the P atom of the active isomer (II) is in the *R* configuration. Recently, Pikul *et al.* (1999) reported that a phosphinamide-based hydroxamate (III) having an *R* configuration at the P atom exhibited inhibitory activities against MMPs, while the *S* isomer at the P atom was a poor inhibitor. As expected, the stereochemistry of the P atom of (II) was consistent with that of (III).



(III)

The structural data of (I) reveal that the non-aromatic portion of the tetrahydroisoquinoline unit adopts a half-chair conformation. The torsion angles C2—C3—C9—C8 and N1—C1—C8—C9 are 29.7 (4) and −9.5 (4)°, respectively. Comparison of the phosphonamide portion of (I) with the corresponding phosphinamide portion of (III) reveals structural differences as follows. The bond lengths around the P atom of (I), P1—O3, P1—N1 and P1—C13 are similar to the corresponding bond lengths of (III), within a range of 0.02 Å. On the other hand, the bond angles around the P atom of (I) are different from those of (III). The O3—P1—C13 bond angle of (I) is larger than the corresponding bond angle of (III) [114.0 (1) and 108.3°, respectively], whereas the O4—P1—C13 and N1—P1—C13 bond angles are smaller than those of (III) [O4—P1—C13 105.5 (1)° for (I) and 108.3° for (III); N1—P1—C13 107.9 (1)° for (I) and 110.5° for (III)]. The P1—C13 bond of (I) leans further towards the N1—P1—O4 plane compared to the situation in (III).

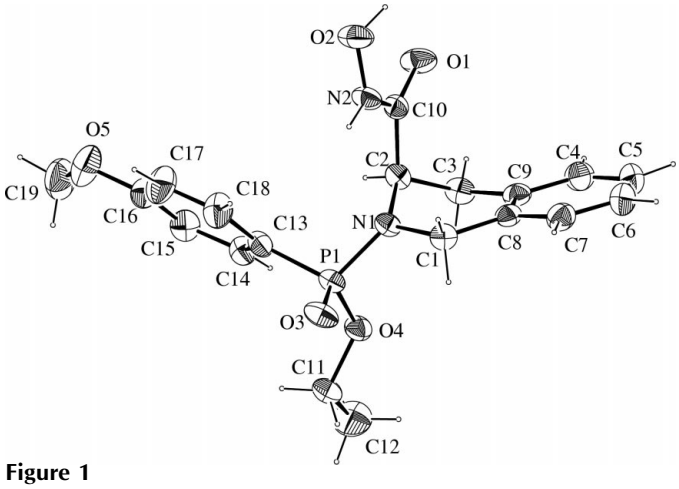


Figure 1
The molecular structure of (I) showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 40% probability level.

Experimental

The synthesis of the title compound is reported elsewhere (Sawa *et al.*, 2001). Crystals of (I) were obtained by recrystallization from EtOH at 293 K. The melting point of (I) is 440.0–440.5 K. The optical rotation of (I), $[\alpha]_D^{20}$, is +68.43° (*c* 1.02, MeOH) and that of (II) is +18.48° (*c* 1.10, MeOH).

Crystal data

$C_{19}H_{23}N_2O_5P$
M_r = 390.37
Orthorhombic, $P2_12_12_1$
a = 10.156 (2) Å
b = 19.733 (1) Å
c = 9.486 (1) Å
V = 1901.1 (3) Å^3
Z = 4
D_x = 1.364 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 21 reflections
θ = 27.5–30.0°
μ = 1.57 mm^{-1}
T = 294.2 K
Prismatic, colorless
0.20 × 0.10 × 0.10 mm

Data collection

Rigaku AFC-5*R* diffractometer
ω–2θ scans
Absorption correction: ψ scan (North *et al.*, 1968)
T_{min} = 0.757, T_{max} = 0.854
3303 measured reflections
3303 independent reflections
2991 reflections with $F^2 > 2\sigma(F^2)$
R_{int} = 0.016
θ_{max} = 62.0°
h = −9 → 11
k = −22 → 22
l = −10 → 10
3 standard reflections
every 150 reflections
intensity decay: 3.7%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.041
$wR(F^2)$ = 0.102
S = 1.65
3303 reflections
313 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + \{0.019[\mathrm{Max}(F_o^2,0) + 2F_c^2]/3\}^2]$
$(\Delta/\sigma)_{max}$ = 0.013
$\Delta\rho_{max}$ = 0.17 e Å^{-3}
$\Delta\rho_{min}$ = −0.20 e Å^{-3}
Absolute structure: Flack (1983), 1571 Friedel pairs
Flack parameter = 0.01 (3)

Table 1
Selected geometric parameters (Å, °).

P1—O3	1.477 (2)	P1—N1	1.636 (3)
P1—O4	1.584 (2)	P1—C13	1.793 (3)
O3—P1—O4	112.6 (1)	O4—P1—N1	104.5 (1)
O3—P1—N1	111.7 (1)	O4—P1—C13	105.5 (1)
O3—P1—C13	114.0 (1)	N1—P1—C13	107.9 (1)
N1—C1—C8—C9	−9.5 (4)	C2—C3—C9—C8	29.7 (4)

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

D—H···A	D—H	H···A	D···A	D—H···A
O2—H11···O1	0.90 (4)	2.44 (3)	2.701 (2)	97 (2)
N2—H10···N1	0.88 (3)	2.46 (2)	2.703 (2)	96 (1)
N2—H10···O1^{i}	0.88 (3)	2.12 (2)	2.951 (2)	158 (2)

Symmetry code: (i) $\frac{1}{2}+x, \frac{3}{2}-y, 1-z$.

The maximum θ was restricted to 62° by the diffractometer geometry. The methyl H atoms on C12 and C19 were placed at geometrically idealized positions (C—H = 0.95 Å) and not refined. All other H atoms were found from the difference Fourier maps and refined isotropically. The C—H, N—H and O—H bond lengths are 0.90 (3)–1.07 (4), 0.88 (3) and 0.90 (4) Å, respectively.

Data collection: *Rigaku/AFC Diffractometer Control Software* (Rigaku, 1998); cell refinement: *Rigaku/AFC Diffractometer Control Software*; data reduction: *teXsan* (Molecular Structure Corporation, 1999); program(s) used to solve structure: *SIR*92 (Altomare *et al.*, 1994); program(s) used to refine structure: *teXsan*; molecular graphics: *ORTEP*II (Johnson, 1976); software used to prepare material for publication: *teXsan*.

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