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(3*R*,4*S*)-*cis*-3-Acetoxy-1-(4-methoxyphenyl)-4-(2-furanyl)azetidin-2-one

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Key indicators

Single-crystal X-ray study
T = 293 K
Mean σ(C–C) = 0.004 Å
R factor = 0.037
wR factor = 0.105
Data-to-parameter ratio = 9.1

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

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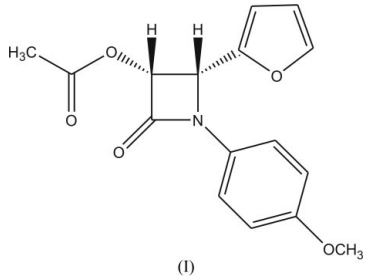
The enantiopure title compound, $C_{16}H_{15}NO_5$, was obtained, together with its hydrolysed (3*S*,4*R*)-enantiomer, by resolution of racemic *cis*-3-acetoxy-1-(4-methoxyphenyl)-4-(2-furanyl)azetidin-2-one using a native enzyme MTCC 5125. The two H atoms on the azetidinone ring are sited in a *cis* configuration above the plane of the β-lactam ring, as indicated by ^{1}H NMR.

Comment

Recently, α-hydroxy-β-lactams have attracted much attention because they are convenient intermediates for the semi-synthesis of the antitumour drug Taxol (Paclitaxel), Taxotere (Docletaxel) and other bioactive analogues (Hattori & Yamamoto, 1994; Ojima, 1995; Kanazawa *et al.*, 1993; Brieva *et al.*, 1993). β–Lactams are also versatile synthons for amino acids, alkaloids and natural products, and are key intermediates in the synthesis of biologically active antibiotics (Jayaram *et al.*, 1997; Nagahara & Kametani, 1987; Dürckheimer *et al.*, 1985). They have also been recognized as precursors of various non-β-lactam derivatives (Manhas *et al.*, 1976; Ojima *et al.*, 1992; Ojima, 1993).



(I)

The title compound, (I), was prepared by the Staudinger reaction using a Schiff base and acetoxyacetyl chloride, and resolved by a native enzyme (chiral HPLC) in 99% enantiopurity. Its structure has now been confirmed by X-ray structural analysis. Holton & Vu (2003) have also resolved other azetidinone derivatives using beef liver suspension. The *cis* configuration of the C3 and C4 H atoms in (I) is in accordance with their strong ^{1}H NMR coupling (J = 4.73 Hz) in $CDCl_3$ solution. Interplanar angles of 1.6 (2) and 83.4 (1)° are observed between the β-lactam ring and its 4-methoxyphenyl and furanyl substituents, respectively. As a result of the partial double-bond character of the amide bond N1—C2 [1.369 (3) Å], the C11—N1—C2 angle of 134.1 (2)° is markedly wider than the adjacent C11—N1—C4 angle [130.6 (2)°].

Experimental

Racemic *cis*-3-acetoxy-1-(4-methoxyphenyl)-4-(2-furanyl)azetidin-2-one (1 equivalent) and lipase enzyme (MTCC 5125) (0.2 equivalent,

lypholysed powder) in the presence of DMF (10%, *v*/*v* buffer) were stirred in phosphate buffer (0.1 *M*, pH 7.0) for 5 h at 298 K. After the required hydrolysis, the reaction mixture was extracted with ethyl acetate. The organic phase was washed with water, dried over sodium sulfate and chromatographed on a silica-gel column to furnish optically pure (I) and its hydrolysed (3*S*,4*R*)-isomer in an overall yield of 92%. The title compound was analyzed for $C_{16}H_{15}NO_5$ (calculated: C 63.76, H 5.02, N 4.65%; found: C 63.81, H 5.07, N 4.66%) and its chemical structure established on the basis of its spectroscopic data. ^{1}H NMR (Bruker, 500 MHz, $CDCl_3$): δ 1.93 (*s*, 3H, $-OCOCH_3$), 3.76 (*s*, 3H, $-OCH_3$), 5.39 (*d*, 1H, *J* = 4.72 Hz, C_4-H), 5.95 (*d*, 1H, *J* = 4.73 Hz, C_3-H), 6.39 (dd, 1H, *J* = 3.19 and 1.36 Hz, furanyl C_4-H), 6.43 (*d*, 1H, *J* = 3.21 Hz, furanyl C_3-H), 6.83 (*d*, 2H, *J* = 9.00 Hz, Ar-H), 7.29 (*d*, 2H, *J* = 9.00 Hz, Ar-H), 7.45 (*d*, 1H, *J* = 0.97 Hz, furanyl C_5-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.01, 55.32, 55.45, 76.10, 110.83, 110.84, 114.41, 118.61, 130.22, 143.62, 146.77, 156.73, 161.03, 169.36. FT–IR (Bruker, KBr) ν (cm^{-1}) = 3476 (*m*), 2959 (*m*), 1743 (*s*), 1590 (*w*), 1516 (*s*), 1378 (*s*), 1301 (*m*), 1229 (*s*), 1153 (*m*), 1066 (*m*), 832 (*s*). MS/MS (Thermo Finnigan TSQ5000): *m*/*z* (%) = 301.9 (10) $(M + H)^+$, 259.8 (18), 241.9 (100), 213.9 (45), 201.8 (23), 185.9 (8), 152.9 (11), 110.9 (8). (I) was crystallized from a mixture of dichloromethane and *n*-hexane (19:1) [m.p. 432–434 K (uncorrected), $[\alpha]^{30}D$ = (+) 13.6° (*c* 1, $CHCl_3$)]. Crystals of (I) suitable for single-crystal X-ray diffraction were selected directly from the sample as prepared.

Crystal data

$C_{16}H_{15}NO_5$	D_x = 1.337 Mg m^{-3}
M_r = 301.29	Mo $K\alpha$ radiation
Monoclinic, $P2_1$	Cell parameters from 15 reflections
a = 5.459 (3) Å	θ = 7.5–15°
b = 8.011 (3) Å	μ = 0.10 mm^{-1}
c = 17.205 (5) Å	T = 293 (2) K
β = 96.00 (3)°	Prism, colourless
V = 748.3 (5) $Å^3$	0.52 × 0.51 × 0.40 mm
Z = 2	

Data collection

Siemens *P*4 four-circle diffractometer	1592 reflections with $I > 2\sigma(I)$
Profile-fitted ω scans	R_{int} = 0.023
Absorption correction: ψ scan (*XPREP* in *SHELXTL-Plus*; Sheldrick, 1995)	θ_{max} = 27.5°
T_{min} = 0.930, T_{max} = 0.962	$h = -7 \rightarrow 0$
2019 measured reflections	$k = 0 \rightarrow 10$
1833 independent reflections	$l = -22 \rightarrow 22$
	3 standard reflections every 100 reflections
	intensity decay: 2%

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0627P)^2 + 0.0621P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)]$ = 0.037	$(\Delta/\sigma)_{max} < 0.001$
$wR(F^2)$ = 0.105	$\Delta\rho_{max}$ = 0.17 e $Å^{-3}$
S = 1.04	$\Delta\rho_{min}$ = −0.17 e $Å^{-3}$
1833 reflections	Extinction correction: *SHELXL*97
202 parameters	Extinction coefficient: 0.025 (6)
H-atom parameters constrained	

All H atoms were visible in difference maps and subsequently refined as riding atoms, with C—H distances of 0.93 (aromatic CH), 0.96 (CH_3) or 0.98 Å (CH). In the absence of any significant anomalous scattering, the Flack (1983) parameter was indeterminate (Flack & Bernardinelli, 2000) for Mo Kα radiation. Hence, no Friedel-related intensities were collected for Mo radiation and the absolute configuration was set by reference to the known chirality of the enantiopure title compound. The chirality of (I) was also independently confirmed by collection of a Cu Kα data set (θ_{max} = 65.48°, R = 0.047, $wR(F^2)$ = 0.128 for 1896 unique reflections including Friedel pairs), which yielded an Flack (1983) parameter of x = 0.0 (3) for the correct 3*R*,4*S* formulation.

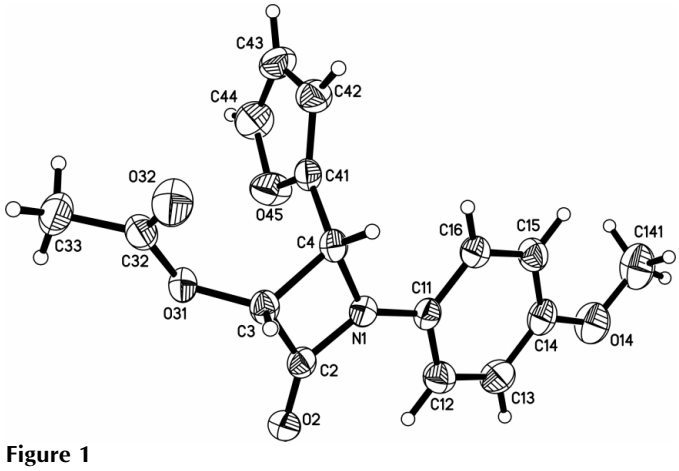


Figure 1
The moleclar structure of (I), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level.

Data collection: *R*3*m*/*V User's Guide* (Siemens, 1989); cell refinement: *R*3*m*/*V User's Guide*; data reduction: *XDISK* in *R*3*m*/*V User's Guide*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *SHELXTL-Plus* (Sheldrick, 1995); software used to prepare material for publication: *SHELXL*97.

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