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(3*S*,4*R*)-4-[4-(Benzyloxy)phenyl]-3-(4-fluorophenyl)-1-[(*S*)-1-(4-methoxyphenyl)ethyl]azetidin-2-one

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Key indicators

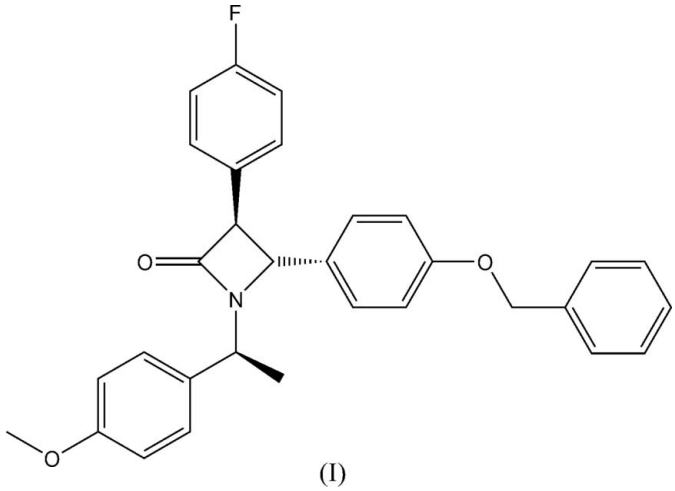
Single-crystal X-ray study
T = 293 K
Mean σ(C–C) = 0.006 Å
R factor = 0.046
wR factor = 0.133
Data-to-parameter ratio = 9.2

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

The title compound, $C_{31}H_{28}FNO_3$, is an intermediate in the synthesis of ezetimibe analogues. The absolute configuration has been established on the basis of an unchanging chiral centre in one reactant.

Comment

Ezetimibe is a drug approved by the US Food and Drug Administration (FDA) for use either alone or in combination with a statin to reduce the levels of blood cholesterol (Rosenblum *et al.*, 1998). The title compound, (I), is an intermediate in one of our syntheses of ezetimibe analogues. It was prepared *via* a Staudinger reaction (Palomo *et al.*, 1999) using a chiral Schiff base and phenylacetoxyacetyl chloride. Two diastereomers of (I) were separated by flash chromotography, and X-ray structure analysis was undertaken for one of these to determine the absolute configuration of the products. On the basis of the known *S* configuration for the chiral centre at C23, the remaining chiral centres are shown to be *R* (C14) and *S* (C15).



(I)

Experimental

A mixture of 4-benzyloxybenzaldehyde (0.095 mol) and (*S*)-1-(4-methoxyphenyl)ethanamine (0.095 mol) in benzene (300 ml) was refluxed for 6 h with azeotropic removal of water *via* a Dean–Stark trap. The mixture was cooled to room temperature and concentrated *in vacuo*. Anhydrous toluene (300 ml) and triethylamine (0.19 mol) were added, the solution was heated to reflux, and 2-(4-fluorophenyl)acetyl chloride (0.095 mol) dissolved in 50 ml toluene was added dropwise to the refluxing solution over a period of 7 h. After a further 12 h, the reaction mixture was cooled to room temperature, acidified

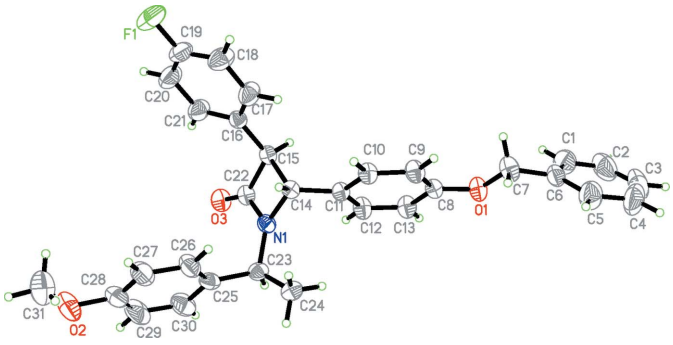


Figure 1
The molecular structure of (I), with displacement ellipsoids drawn at the 30% probability level for non-H atoms.

with 1 *N* HCl(aq) (200 ml), and diluted with ethyl acetate. The organic layer was separated, washed twice with 1 *N* HCl(aq) and twice with water, dried over $MgSO_4$, and concentrated to afford the crude azetidinone product. Purification by flash chromatography using petroleum ether/ethyl acetate (7:1) elunt afforded the title compound as two diastereomers. One diastereomer was crystallized slowly from a mixture of methanol and dichloromethane (2:1) at 298 K.

Crystal data

$C_{31}H_{28}FNO_3$
M_r = 481.54
Monoclinic, $P2_1$
a = 5.9709 (12) Å
b = 14.377 (3) Å
c = 14.905 (3) Å
β = 92.64 (3)°
V = 1278.2 (4) Å^3
Z = 2
Mo $K\alpha$ radiation
μ = 0.09 mm^{-1}
T = 293 (2) K
0.31 × 0.31 × 0.28 mm

Data collection

Rigaku R-AXIS RAPID diffractometer
Absorption correction: multi-scan (*ABSCOR*; Higashi, 1995)
T_{min} = 0.974, T_{max} = 0.977
6874 measured reflections
3017 independent reflections
1770 reflections with $I > 2\sigma(I)$
R_{int} = 0.032

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.046
$wR(F^2)$ = 0.133
S = 0.93
3017 reflections
327 parameters
7 restraints
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.16 e Å^{-3}
$\Delta\rho_{min}$ = −0.14 e Å^{-3}
Absolute structure: assigned on the basis of unchanging chiral centre

H atoms were positioned geometrically (C—H = 0.93–0.98 Å) and treated as riding, with U_{iso}(H) = 1.2U_{eq}(C), or 1.5U_{eq}(C) for the methyl groups. The methyl groups were allowed to rotate about their local threefold axes. The displacement parameters of C31 were restrained to approximate isotropic behaviour. In the absence of significant anomalous scattering, Friedel pairs have been merged as equivalent data.

Data collection: *RAPID-AUTO* (Rigaku, 1999); cell refinement: *RAPID-AUTO*; data reduction: *CrystalStructure* (Rigaku/MSC, 2002); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *PLATON* (Spek, 2003); software used to prepare material for publication: *SHELXL97*.

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