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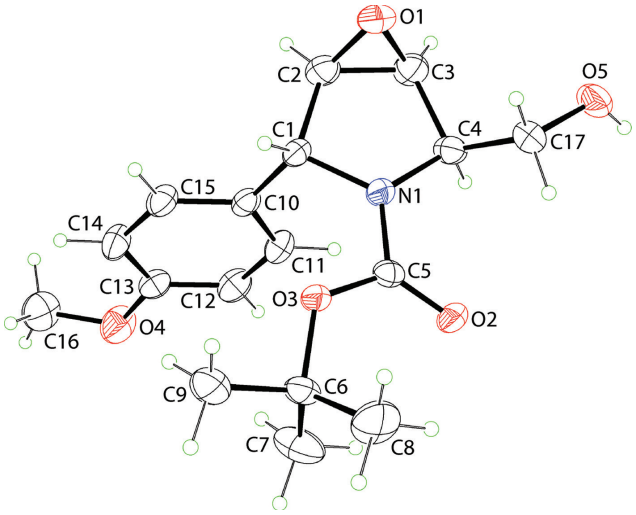
Crystal structure of *tert*-butyl (1*S*,2*R*,5*R*)-2-(hydroxymethyl)-4-(4-methoxyphenyl)-6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylate, $C_{17}H_{23}NO_5$



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Abstract

$C_{17}H_{23}NO_5$, monoclinic, $P2_1$ (no. 4), $a = 6.0479(9)$ Å, $b = 9.7032(10)$ Å, $c = 14.711(2)$ Å, $\beta = 94.174(9)°$, $V = 861.0(2)$ Å^3, $Z = 2$, $R_{gt}(F) = 0.0440$, $wR_{ref}(F^2) = 0.1436$, $T = 293(2)$ K.

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The molecular structure is shown in the figure. Table 1 contains crystallographic data and Table 2 contains the list of the atoms including atomic coordinates and displacement parameters.

Table 1: Data collection and handling.

Crystal:	Colourless irregular
Size:	0.13 × 0.11 × 0.08 mm
Wavelength:	Mo $K\alpha$ radiation (0.71073 Å)
μ:	0.09 mm^{-1}
Diffractometer, scan mode:	Enraf Nonius TurboCAD4, ω
θ_{max}, completeness:	28.0°, >99%
$N(hkl)_{measured}$, $N(hkl)_{unique}$:	2373, 2177
Criterion for I_{obs}, $N(hkl)_{gt}$:	$I_{obs} > 2\ \sigma(I_{obs})$, 959
$N(param)_{refined}$:	215
Programs:	CAD4 [1, 2], SIR2014 [3], SHELX [4], WinGX/ORTEP [5]

Table 2: Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2).

Atom	*x*	*y*	*z*	U_{iso}*/U_{eq}
O1	1.0955(5)	0.6239(4)	0.0462(2)	0.0737(10)
O2	0.5436(4)	0.6809(3)	0.26247(18)	0.0562(8)
O3	0.8850(4)	0.7300(3)	0.32798(15)	0.0470(7)
O4	1.0024(6)	1.3511(4)	0.2627(3)	0.0834(11)
O5	0.5175(6)	0.4999(4)	0.0060(3)	0.0825(11)
H5O	0.386(4)	0.520(9)	−0.005(5)	0.124*
N1	0.8400(5)	0.7118(4)	0.1783(2)	0.0453(8)
C1	1.0518(6)	0.7865(4)	0.1710(3)	0.0454(9)
H1	1.170684	0.742274	0.209306	0.055*
C2	1.0881(7)	0.7658(5)	0.0721(3)	0.0617(12)
H2	1.174220	0.833775	0.040294	0.074*
C3	0.8958(7)	0.7032(6)	0.0251(3)	0.0631(13)
H3	0.852173	0.728652	−0.038120	0.076*
C4	0.7210(7)	0.6772(5)	0.0911(2)	0.0525(11)
H4	0.595957	0.740386	0.078668	0.063*
C5	0.7387(6)	0.7058(4)	0.2575(2)	0.0430(9)
C6	0.8162(7)	0.7445(5)	0.4208(2)	0.0542(11)
C7	0.6751(11)	0.8712(7)	0.4258(4)	0.098(2)
H7A	0.748015	0.947657	0.399407	0.147*
H7B	0.652611	0.891178	0.488413	0.147*
H7C	0.534339	0.855684	0.392915	0.147*

Table 2 (continued)

Atom	x	y	z	U_{iso}*/U_{eq}
C8	0.6988(11)	0.6165(7)	0.4494(4)	0.095(2)
H8A	0.554585	0.611799	0.417677	0.142*
H8B	0.683596	0.619360	0.513913	0.142*
H8C	0.783320	0.536737	0.434955	0.142*
C9	1.0359(8)	0.7616(8)	0.4745(3)	0.0879(19)
H9A	1.123476	0.679990	0.468595	0.132*
H9B	1.011915	0.776331	0.537546	0.132*
H9C	1.112638	0.839414	0.451570	0.132*
C10	1.0365(7)	0.9373(4)	0.1948(3)	0.0455(10)
C11	0.8468(7)	1.0142(5)	0.1799(3)	0.0547(11)
H11	0.719007	0.971968	0.154278	0.066*
C12	0.8402(8)	1.1503(5)	0.2015(3)	0.0634(13)
H12	0.709571	1.199820	0.189666	0.076*
C13	1.0254(7)	1.2152(5)	0.2406(3)	0.0545(11)
C14	1.2181(8)	1.1414(6)	0.2567(3)	0.0659(13)
H14	1.345316	1.183853	0.282606	0.079*
C15	1.2205(7)	1.0023(5)	0.2336(3)	0.0566(11)
H15	1.350808	0.952274	0.244859	0.068*
C16	1.1937(11)	1.4287(6)	0.2830(5)	0.0895(18)
H16A	1.277934	1.388420	0.334169	0.134*
H16B	1.153392	1.521280	0.297749	0.134*
H16C	1.281566	1.429701	0.231259	0.134*
C17	0.6391(8)	0.5282(5)	0.0889(3)	0.0656(13)
H17A	0.764869	0.466211	0.096364	0.079*
H17B	0.546265	0.512817	0.138970	0.079*

Source of material

A 77% solution of *m*-chloroperbenzoic acid (CPBA; 3.67 g, 16.374 mmol) was dissolved in CH_2Cl_2 (30 mL). The water contained in the CPBA solution was separated with the aid of a separation funnel. The organic phase was added over a solution of *tert*-butyl (2*S*,5*S*)-2-(hydroxymethyl)-5-(4-methoxyphenyl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate (1.0 g, 3.275 mmol) in CH_2Cl_2 (10 mL), containing anhydrous $NaHCO_3$ (1.65 g, 19.648 mmol) as a buffer. The suspension was stirred for 24 h at room temperature. The reaction was stopped by adding a saturated $NaHSO_3$ (15 mL) solution and the mixture was extracted with EtOAc. The phases were separated and the organic phase was washed with saturated $NaHCO_3$ solution (2 × 15 mL) and NaCl (15 mL). The organic phase was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel, using an EtOAc/*n*-hexane elution gradient (1:2, 1:1 and 2:1). The title epoxide (I) was obtained as a white solid in 73% yield (765 mg), with a diastereoselectivity of 100% [6]. **M.pt:** 380–382 K. Crystals of (I) were obtained by slow evaporation of its $CHCl_3$ solution. The ^{1}H and ^{13}C NMR spectra reflect the presence of conformational rotamers in solution. **^{1}H NMR** (300 MHz, $CDCl_3$ r.t.): δ = 7.08 (d, *J* = 8.8 Hz, 2H); 6.88 (d, *J* = 8.8 Hz, 2H); 4.91 (s, 1H); 4.20 (dt, *J* = 6.6 and 2.2 Hz, 1H); 4.08 (dd, *J* = 12.4 and 2.2 Hz, 1H); 3.96 (dd, *J* = 12.4 and 6.6 Hz, 1H); 3.84 (m, 1H); 3.83–3.77 (overlapped signal, 1H); 3.80 (s, 3H); 3.43 (d, *J* = 2.9 Hz, 1H); 1.40 (s, 0.5H); 1.18 (s, 8.5H). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$, r.t.): δ = 159.2; 156.3; 130.9; 127.6 ; 114.0; 80.9; 64.1; 63.7; 62.6; 58.1; 57.6; 55.2; 28.2; 28.0. **HRMS** Calc for $C_{17}H_{23}NO_5$: 321.15762; found 321.15708.

Experimental details

The C-bound H atoms were geometrically placed (C—H = 0.93–0.98 Å) and refined as riding with U_{iso}(H) = 1.2–1.5U_{eq}(C). The O-bound H atom was refined with O—H = 0.82 ± 0.01 Å, and with 1.5U_{eq}(O). The absolute structure was not determined in the X-ray experiment but, the assignment of stereochemistry at the four chiral centres is based on the chirality of the synthetic precursor employed in the synthesis.

Comment

The title β-epoxypyrrolidine derivative, (I), is a key precursor for the formation of a salt, 3′-deoxy-radicamine-A hydrochloride [6]. In [6], compound (I) was prepared by the epoxidation reaction of tert-butyl (2*S*)-2-(hydroxymethyl)-5-(4-methoxyphenyl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate with *m*-chloroperbenzoicacid (CPBA). Subsequently, the opening of (I) in a dioxane/water/H_2SO_4 mixture (3:2:0.2), at reflux temperature, was totally regioselective. After purification using Dowex-H^+, followed by treatment with a 2.5N HCl solution, the desired 3′-deoxy-radicamine-A hydrochloride was obtained in 80% yield. This product is a crucial precursor for the preparation of the (natural product) pyrrolidine alkaloids Radicamines A and B [7] which are of interest as inhibitors of α-glucosidase. The inhibition of α-glucosidase is key for the treatment of type 2 diabetes mellitus but, also for other disease such as cancer [8]. Herein, the crystal and molecular structures of precursor (I) are described.

The molecular structure of (I) is illustrated in the figure (25% displacement ellipsoids) and is constructed about a β-epoxypyrrolidine core. The conformation of the five-membered ring is an envelope with the N1 atom being the flap atom. The r.m.s. deviation of the four constituent carbon atoms is 0.003 Å and the N1 atom lies 0.195(6) Å out of the plane. The dihedral angle between the least-squares plane of the four carbon atoms and the plane through the epoxy ring is 74.4(3)°. The N1 is bound by a *tert*-butyloxycarbonyl group with the N1—C5—O2—C6 torsion angle of 173.3(3)° indicative of a co-planar system. A close to trigonal geometry about the N1 atom is indicated by the sum of the angles subtended at the N1 atom of 358.2°. The five-membered ring is penta-substituted with the C1 and C4 atoms flanking the N1 atom bearing 4-methoxyphenyl and hydroxymethyl substituents,

respectively. The configurations at the C1–C4 atoms are *R*, *R*, *S* and *R*.

There is a single literature precedent for (I) which was described only recently [9]. Here, the difference arises as the N1-bound group is ethyloxycarbonyl and the hydroxymethyl group of (I) is no longer present. The five-membered ring is an envelope, as in (I), and the dihedral angle between the rings comprising the β-epoxypyrrolidine core is 78.53(10)° [9].

In the crystal, a linear supramolecular chain along the *a*-axis is formed through hydroxyl-O—H···O(epoxy) hydrogen bonding [O5—H5o···O1^{i}: H5o···O1^{i} = 2.21(5) Å, O5···O1^{i} = 2.921(5) Å with angle at H5o = 145(7)° for symmetry operation (i): $-1+x$, y, z]. The chains thus formed, are connected into a supramolecular layer in the *ab*-plane by methylene-C—H···O(carbonyl, hydroxyl) interactions [C1—H1···O2^{ii}: H1···O2^{ii} = 2.41 Å, C1···O2^{ii} = 3.335(5) Å with angle at H1 = 158° and C2—H2···O5^{iii}: H2···O5^{iii} = 2.59 Å, C2···O5^{iii} = 3.545(6) Å with angle at H2 = 164° for (ii) $1+x$, y, z and (iii) $2-x$, $1/2+y$, $-z$]. The layers inter-digitate along the *c*-axis direction so the *tert*-butyl groups are off-set and occupy the space in the inter-layer region.

Further insight into the molecular packing was accomplished by calculating the Hirshfeld surface as well as the full and decomposed two-dimensional fingerprint plots using Crystal Explorer 17 [10] and literature procedures [11]. The most distinctive feature of the overall fingerprint plot were sharp spikes ascribed to the O—H···O hydrogen bonding. Indeed, H···O/O···H contacts contributed 22.4% to the overall surface but, by far, the major contributions come from H···H contacts at 70.9%, the large number reflecting to a great extent the occupancy of the inter-layer region by *tert*-butyl groups. The only other significant contribution to the surface comes from H···C/C···H contacts at 5.9%.

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References

1. CAD4 Express Software. Enraf-Nonius, Delft, The Netherlands (1994).
2. Harms, K.; Wocadlo, S.: XCAD4 – CAD4 Data Reduction. Program for Processing CAD-4 Diffractometer Data. University of Marburg, Germany, 1995.
3. Burla, M. C.; Caliandro, R.; Carrozzini, B.; Cascarano, G. L.; Cuocci, C.; Giacovazzo, C.; Mallamo, M.; Mazzone, A.; Polidori, G.: Crystal structure determination and refinement via SIR2014. J. Appl. Cryst. **48** (2015) 306–309.
4. Sheldrick, G. M.: Crystal structure refinement with SHELXL. Acta Crystallogr. **C71** (2015) 3–8.
5. Farrugia, L. J.: WinGX and ORTEP for Windows: an update. J. Appl. Cryst. **45** (2012) 849–854.
6. Garcia, A. L. L.: PhD thesis, Universidade Estadual de Campinas, UNICAMP, Campinas, SP, Brazil, 2008.
7. Shibano, M.; Tsukamato, D.; Masuda, A.; Tanaka, Y.; Kusano, G.: Two new pyrrolidine alkaloids, Radicamines A and B, as inhibitors of α-glucosidase from Lobelia chinensis LOUR. Chem. Pharm. Bull. **49** (2001) 1362–1365
8. Dhameja, M.; Gupta, P.: Synthetic heterocyclic candidates as promising α-glucosidase inhibitors: an overview. Eur. J. Med. Chem. **176** (2019) 343–377.
9. Zukerman-Schpector, J.; Sugiyama, F. H.; Garcia, A. L. L.; Correia, C. R. D.; Jotani, M. M.; Tiekink, E. R. T.: Ethyl 2-(4-methoxyphenyl)-6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylate: crystal structure and Hirshfeld analysis. Acta Crystallogr. **E73** (2017) 1218–1222.
10. Turner, M. J.; McKinnon, J. J.; Wolff, S. K.; Grimwood, D. J.; Spackman, P. R.; Jayatilaka, D.; Spackman, M. A.: Crystal Explorer v17. The University of Western Australia, Australia (2017).
11. Tan, S. L.; Jotani, M. M.; Tiekink, E. R. T.: Utilizing Hirshfeld surface calculations, non-covalent interaction (NCI) plots and the calculation of interaction energies in the analysis of molecular packing. Acta Crystallogr. **E75** (2019) 308–318.