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Relative configuration, absolute configuration and absolute structure of three isomeric 8-benzyl-2-[(4-bromophenyl)(hydroxy)methyl]-8-azabicyclo[3.2.1]octan-3-ones

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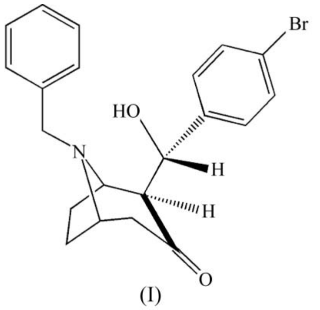
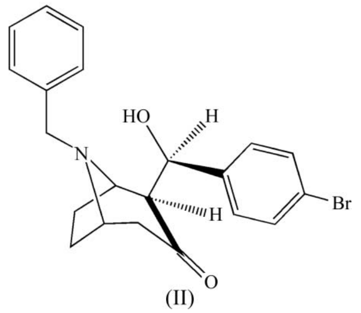
The title compounds, $C_{21}H_{22}BrNO_2$, are isomeric 8-benzyl-2-[(4-bromophenyl)(hydroxy)methyl]-8-azabicyclo[3.2.1]octan-3-ones. Compound (I), the (±)-*exo*,*syn*-(1*RS*,2*SR*,5*SR*,9*SR*) isomer, crystallizes in the hexagonal space group $R\overline{3}$, while compounds (II) [the (+)-*exo*,*anti*-(1*R*,2*S*,5*S*,9*R*) isomer] and (III) [the (±)-*exo*,*anti*-(1*RS*,2*SR*,5*SR*,9*RS*) isomer] crystallize in the orthorhombic space groups $P2_12_12_1$ and $Pna2_1$, respectively. The absolute configuration was determined for enantiomerically pure (II). For the noncentrosymmetric crystal of (III), its absolute structure was established. In the crystal structures of (I) and (II), an intramolecular hydrogen bond is formed between the hydroxy group and the heterocyclic N atom. In the crystal structure of racemic (III), hydrogen-bonded chains of molecules are formed *via* intermolecular O—H···O interactions. Additionally, face-to-edge π–π interactions are present in the crystal structures of (I) and (II). In all three structures, the piperidinone rings adopt chair conformations and the *N*-benzyl substituents occupy the equatorial positions.

Comment

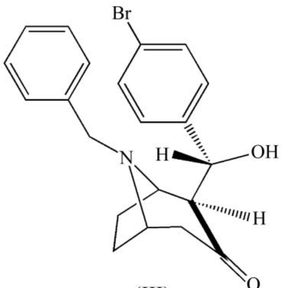
Tropane (8-methyl-8-azabicyclo[3.2.1]octane) and nortropane (8-azabicyclo[3.2.1]octane) scaffolds can be found in numerous natural alkaloids, many of which demonstrate a range of biological activities (Lounasmaa, 1988; Lounasmaa & Tamminen, 1993). Several tropane alkaloids and their non-natural analogues have been synthesized in the quest for interesting properties suitable for agrochemical and pharmaceutical applications (Singh, 2000; Zhao *et al.*, 2000; Xu *et al.*, 2002; Pollini *et al.*, 2006). Diastereomerically and enantiomerically pure aldols of tropinone are key intermediates used by us in the stereoselective syntheses of knightinol, alkaloid KD-B (Majewski & Lazny, 1995) and ferrugine (Sienkiewicz *et al.*, 2009; Lazny, Sienkiewicz, Olenski *et al.*, 2012), as well as by others for the synthesis of the nonnatural enantiomer of cocaine (*ent*-cocaine) (Lee *et al.*, 2000). However, the stereoselective syntheses of nortropinone aldols (Lazny *et al.*, 2001; Lazny & Nodzewska, 2003; Lazny *et al.*, 2010) were not so effective. Possible approaches to obtaining nor derivatives have used synthetic equivalents of nortropinone, including triazene derivatives (Lazny *et al.*, 2001, 2010; Lazny & Nodzewska, 2003), urethane derivatives (Lazny *et al.*, 2010) and polymer-supported analogues (Lazny *et al.*, 2006, 2010; Sienkiewicz & Lazny, 2010). We now report the crystal structures of the three title stereoisomeric forms, (I)–(III), of a promising newly prepared *N*-benzyl-protected derivative.



(I)



(II)



(III)

By analogy with the recently reported spontaneous reaction of an *N*-methyl derivative, *i.e.* tropinone, with aldehydes in the presence of water, which surprisingly gave the other, atypical, diastereomer (Lazny, Nodzewska, & Tomczuk, 2011; Lazny, Nodzewska, Sidorowicz & Kalicki, 2012; Lazny, Ratkiewicz, Nodzewska & Wysocka, 2012), we succeeded in converting a much less reactive *N*-benzyl derivative and an aromatic aldehyde to an aldol product. Based on NMR data, we identified (Lazny, Nodzewska, Sidorowicz & Kalicki, 2012), with high probability, the major product of the reaction as the *exo*,*syn* isomer. Analogous to previous reports, the major product of the reaction promoted by a lithium amide (*e.g.* lithium diisopropylamide, LDA) was assigned the likely

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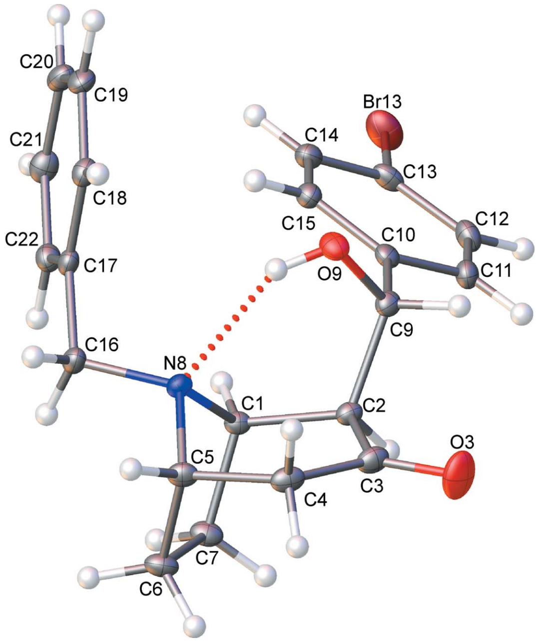

Figure 1
The molecular structure of (I), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level. The dashed line indicates the intramolecular hydrogen bond.

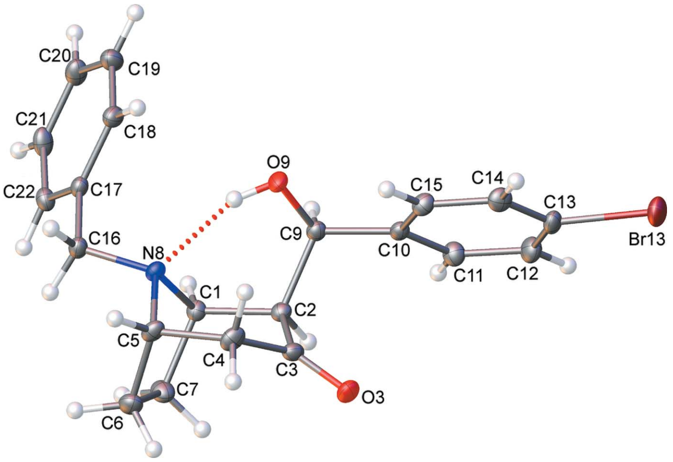

Figure 2
The molecular structure of (II), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level. The dashed line indicates the intramolecular hydrogen bond.

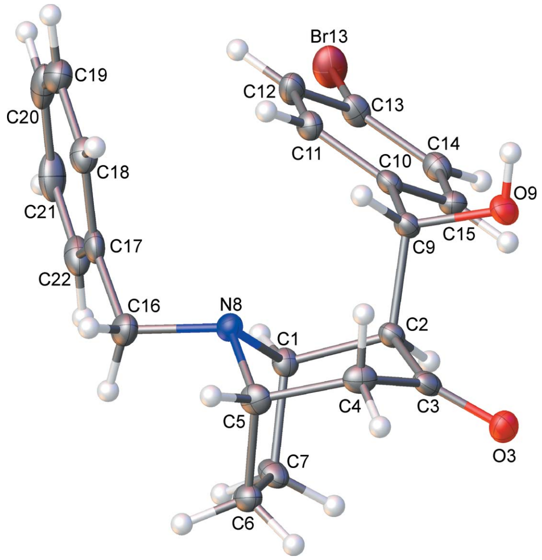

Figure 3
The molecular structure of (III), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level.

exo,*anti* configuration (Lazny *et al.*, 2010; Lazny, Sienkiewicz, Olenski *et al.*, 2012), but the tentative assignments needed to be confirmed. In order to prepare an enantiomerically pure *N*-benzyl analogue of tropinone aldol, we used known enantioselective deprotonation with chiral lithium amide bases (O'Brien, 1998; Simpkins & Weller, 2010). The procedure gave an enantiomerically pure crystalline aldol (likely the *exo*,*anti* isomer), the absolute structure of which reflects the preferred enantio-differentiation of enantiotopic H atoms of the *N*-benzyltropinone system by the chiral lithium amide used (O'Brien, 1998; Simpkins & Weller, 2010; Majewski & Lazny, 1995). From the asymmetric synthesis point of view, it is essential to know the sense of the enantioselection. Therefore, it is crucial not only to determine unambiguously the relative structures of the aldols but also, more importantly, to determine positively the absolute configuration of the product resulting from the reaction of *N*-benzylnortropinone with the specific enantiomeric form of the chiral reagent used.

Based on the present crystallographic studies, the relative configuration of (I) was established. The absolute configuration of (II) and the absolute structure of the crystal of (III) were determined unequivocally based on anomalous diffraction effects, as confirmed by the observed Flack parameters.

In the crystal structure of (I) (Fig. 1), the piperidinone ring of the tropinone system adopts a distorted chair conformation with puckering parameters Q = 0.6536 (18) Å, θ = 43.51 (17)° and φ = 5.8 (3)° (Cremer & Pople, 1975). A chair conformation of the piperidinone ring is observed in the crystal structures of (II) and (III) (Figs. 2 and 3), as is observed in other *N*-methyl and *N*-benzyl derivatives of tropinone and granatanone (Li *et al.*, 1993; Lazny, Wolosewicz, Zielinska *et al.*, 2011; Lazny, Nodzewska, Sidorowicz & Kalicki, 2012; Lazny, Wolosewicz, Dauter & Brzezinski, 2012; Lazny, Sienkiewicz, Olenski *et al.*, 2012; Brzezinski *et al.*, 2012; Jiang *et al.*, 2012). The puckering parameters of the six-membered heterocyclic ring are Q = 0.643 (2) Å, θ = 27.07 (18)° and φ = 6.5 (4)° for (II), and Q = 0.650 (3) Å, θ = 20.4 (3)° and φ = 3.5 (9)° for (III).

In the crystal structure of (I), the piperidinone scaffold is remarkably flattened at the C3 pole of the ring. The strained heterocyclic ring conformation is stabilized by an intramolecular O—H$\cdots$N hydrogen bond, as well as by intramolecular [C15—H15$\cdots$*Cg*1, with C15$\cdots$*Cg*1 = 3.391 (2) Å and C15—H15$\cdots$*Cg*1 = 146°] and intermolecular [C11—H11$\cdots$*Cg*2, with C11$\cdots$*Cg*2 = 3.455 (2) Å and C11—H11$\cdots$*Cg*2 = 152°] face-to-edge C—H$\cdots\pi$ interactions [the symmetry-related molecule is at $(y-1, -x+y, -z+1)$]. For (I) and (II), *Cg*1 and *Cg*2 are the centroids of C17–C22 and C10–C15 rings, respectively. Additionally, the 4-bromophenyl group participates in the formation of short Br$\cdots$Br contacts [3.5122 (3) Å] with two symmetry-related molecules at $(y - 1, -x + y, -z)$ and $(x - y + 1, x + 1, -z)$. The intramolecular O—H$\cdots$N hydrogen bond is also observed in (II). Additionally, intermolecular face-to-edge C—Br$\cdots\pi$ interactions [the symmetry-related molecule is at $(x + \frac{1}{2}, -y + \frac{3}{2}, -z + 1)$] are present in the crystal structure of (II) [C13—Br13$\cdots$*Cg*1, with C13$\cdots$*Cg*1 = 5.372 (2) Å and C13—Br13$\cdots$*Cg*1 = 151.83 (7)°].

The *N*-benzyl substituents of (I)–(III) are equatorial, similar to the majority of crystal structures of *N*-alkylnortropanes and the thermodynamic preference for tropanes in solution (Lazny, Ratkiewicz, Nodzewska, Wynimko & Siergiejczyk, 2012). Such a configuration is strongly related to the *exo* orientation of the bulky 4-bromophenyl(hydroxy)methyl groups at atom C2. The existence of the specific *N*-alkyl invertomer can be explained by steric hindrance of the C2 substituent in (I)–(III). Moreover in (I) and (II), an intramolecular hydrogen bond is formed between heterocyclic atom N8 and the OH group (Figs. 1 and 2); in (I), N$\cdots$O = 2.7902 (19) Å and N—H$\cdots$O = 149°, while in (II) the corresponding values are 2.682 (2) Å and 157 (4)°. As a result, in the crystal structures of (I) and (II), the N-equatorial invertomers are additionally stabilized and inversion to the N-axial conformers is not possible. Similar conformations are observed in solution. The H9*C*—C9—C2—H2 torsion angles of −64.1° for (I) and 56.7° for (II) in the solid state correspond, approximately, to the probable angles in solution, estimated using the Karplus correlation of dihedral angles (52 and 58°) and the observed vicinal coupling constants for benzylic carbinol proton signals at 4.88 (*d*, *J* = 2.2 Hz) and 5.04 p.p.m (*d*, *J* = 2.8 Hz), respectively (Karplus, 1959, 1963; Bifulco *et al.*, 2007). This indicates similar conformations of (I) and (II) in solution and in the solid state.

In the crystal structures of (I) and (II), the packing is based mainly on weak intermolecular interactions. A different mechanism is observed in (III), where the –OH group participates in the formation of an intermolecular hydrogen bond with carbonyl atom O3 from a symmetry-related molecule at $(-x + 2, -y + 1, z - \frac{1}{2})$ [O$\cdots$O = 2.874 (3) Å and O—H$\cdots$O = 176°]. Molecules related by 2_1 axes form helices extending along the *c* direction, and a different orientation of the OH group at atom C9 is observed. However, due to the *exo* configuration of the substituent on the bicyclic system, formation of the second *N*-benzyl invertomer is prevented here by the close proximity of the (4-bromophenyl)(hydroxy)methyl group. The H9*C*—C9—C2—H2 torsion angle of 170.2° in (III) corresponds to the conformation which is disfavoured in solution, as indicated by the relevant vicinal coupling constant (*J* = 2.8 Hz) which rules out such a value for the torsion angle.

Note that the mode of stabilization of the *N*-alkyl group in the equatorial position reported here is also likely to be operational in other *N*-methyl-substituted tropinones and also in *N*-benzylgranatanone derivatives (Lazny, Wolosewicz, Zielinska *et al.*, 2011; Lazny, Sienkiewicz, Olenski *et al.*, 2012; Lazny, Wolosewicz, Dauter & Brzezinski, 2012; Brzezinski *et al.*, 2012).

Experimental

The reaction of 4-bromobenzaldehyde (0.093 g, 0.50 mmol) with *N*-benzylnortropinone (0.215 g, 1.00 mmol) in water (1.25 ml) admixed with an organic cosolvent [dimethylformamide (DMF), 0.25 ml], according to the literature procedure of Lazny, Nodzewska & Tomczuk (2011), gave (I), which was crystallized from diethyl ether [yield: 0.116 g, 58%; m.p. 428–429 K (decomposition)]. Crystals suitable for X-ray diffraction analysis were obtained at room temperature by slow evaporation from a heptane solution of (I). ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.61 (*br s*, 1H), 7.49–7.44 (*m*, 3H), 7.40–7.32 (*m*, 2H), 7.30–7.26 (*m*, 2H), 6.80–6.74 (*m*, 2H), 4.88 (*d*, *J* = 2.2 Hz, 1H), 3.70–3.65 (*m*, 1H), 3.62 (*d*, *J* = 12.4 Hz, 1H), 3.49 (*d*, *J* = 12.4 Hz, 1H), 3.40–3.35 (*m*, 1H), 2.96 (*dd*, *J* = 17.0 Hz, 5.1 Hz, 1H), 2.48 (*dt*, *J* = 17.0 Hz, 1.7 Hz, 1H), 2.21–2.27 (*m*, 1H), 2.25–2.15 (*m*, 2H), 1.78–1.67 (*m*, 1H), 1.53–1.42 (*m*, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 210.6, 142.4, 137.3, 131.2, 129.8, 129.1, 128.1, 127.2, 120.5, 75.6, 63.1, 59.9, 58.0, 57.4, 50.5, 27.1, 26.8.

The reaction of 4-bromobenzaldehyde (0.330 g, 1.78 mmol) with *N*-benzylnortropinone (0.333 g, 1.55 mmol) promoted with chiral lithium (*R*)-*N*-benzhydryl-1-phenylethanamide (0.535 g, 1.86 mmol), according to the literature procedure of Lazny, Sienkiewicz, Olenski *et al.* (2012), followed by precipitation from a mixture of dichloromethane and hexane (1:8 *v*/*v*), gave (II) {yield: 0.470 g, 76%, 75% ee [by ^{1}H NMR in the presence of (*R*)-(−)-1-(9-anthryl)-2,2,2-trifluoroethanol]} as a white solid. An analytical sample was recrystallized from dichloromethane–hexane (1:8 *v*/*v*) [m.p. 404–405 K (decomposition); ee $\geq$ 98%; $[\alpha]_D$ at 293 K = 37° (*c* = 0.5, CHCl$_3$, where *c* is the concentration in grams per 100 ml)]. Crystals suitable for X-ray diffraction analysis were obtained at room temperature by slow evaporation from a heptane solution of (II).

The reaction of 4-bromobenzaldehyde (0.213 g, 1.15 mmol) with *N*-benzylnortropinone (0.215 g, 1.00 mmol) promoted with LDA (lithium diisopropylamide; 1.20 mmol), according to the literature procedure of Lazny, Sienkiewicz, Olenski *et al.* (2012), gave (III), which was crystallized from a mixture of heptane and AcOEt (7:1 *v*/*v*) [yield: 0.380 g, 95%; m.p. 421–423 K (decomposition)]. No additional crystallization attempts were required prior to X-ray data collection. ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.50 (*br s*, 1H), 7.45–7.32 (*m*, 7H), 7.12–7.03 (*m*, 2H), 5.04 (*d*, *J* = 2.8 Hz, 1H), 3.74–3.63 (*m*, 3H), 3.60–3.54 (*m*, 1H), 2.78 (*dd*, *J* = 16.0 Hz, 3.3 Hz, 1H), 2.40 (*s*, 1H), 2.38–2.15 (*m*, 3H), 1.72–1.58 (*m*, 2H); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 208.0, 140.7, 137.4, 131.0, 129.0, 128.8, 127.8, 127.3, 121.0, 75.8, 65.0, 64.1, 58.9, 57.0, 51.5, 26.8, 26.4.

The obtained crystals of (I), (II) and (III) were rather large for the microfocus beam, but due to their fragility, any manipulation (*e.g.* cutting) was unfeasible prior to the diffraction experiments.

Isomer (I)

Crystal data

$C_{21}H_{22}BrNO_2$
M_r = 400.31
Trigonal, $R\overline{3}$
a = 29.8145 (5) Å
c = 10.2028 (2) Å
V = 7854.2 (4) Å^3
Z = 18
Mo $K\alpha$ radiation
μ = 2.36 mm^{-1}
T = 100 K
0.54 × 0.46 × 0.29 mm

Data collection

Agilent SuperNova Dual diffractometer
Absorption correction: analytical (*CrysAlis PRO*; Agilent, 2011)
$T_{\min}$ = 0.434, $T_{\max}$ = 0.633
24029 measured reflections
4885 independent reflections
4130 reflections with $I > 2\sigma(I)$
$R_{\rm int}$ = 0.033

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.033$
$wR(F^2) = 0.081$
$S = 1.06$
4885 reflections
227 parameters
H-atom parameters constrained
$\Delta\rho_{\max} = 0.52$ e Å^{-3}
$\Delta\rho_{\min} = -0.67$ e Å^{-3}

Isomer (II)

Crystal data

$C_{21}H_{22}BrNO_2$
$M_r = 400.31$
Orthorhombic, $P2_12_12_1$
$a = 5.96905$ (4) Å
$b = 14.76590$ (9) Å
$c = 20.76083$ (13) Å
$V = 1829.83$ (2) Å^3
$Z = 4$
Mo $K\alpha$ radiation
$\mu = 2.26$ mm^{-1}
$T = 100$ K
0.52 × 0.11 × 0.09 mm

Data collection

Agilent SuperNova Dual diffractometer
Absorption correction: analytical (*CrysAlis PRO*; Agilent, 2011)
$T_{\min} = 0.308$, $T_{\max} = 0.816$
67899 measured reflections
5359 independent reflections
5007 reflections with $I > 2\sigma(I)$
$R_{\rm int} = 0.064$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.033$
$wR(F^2) = 0.080$
$S = 1.04$
5359 reflections
230 parameters
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{\max} = 0.64$ e Å^{-3}
$\Delta\rho_{\min} = -0.48$ e Å^{-3}
Absolute structure: Flack (1983), with 2292 Friedel pairs
Flack parameter: −0.011 (7)

isomer (III)

Crystal data

$C_{21}H_{22}BrNO_2$
$M_r = 400.31$
Orthorhombic, $Pna2_1$
$a = 9.0968$ (4) Å
$b = 32.0680$ (18) Å
$c = 6.1711$ (4) Å
$V = 1800.22$ (17) Å^3
$Z = 4$
Mo $K\alpha$ radiation
$\mu = 2.30$ mm^{-1}
$T = 100$ K
0.80 × 0.09 × 0.07 mm

Data collection

Agilent SuperNova Dual diffractometer
Absorption correction: analytical (*CrysAlis PRO*; Agilent, 2011)
$T_{\min} = 0.726$, $T_{\max} = 0.870$
9954 measured reflections
4327 independent reflections
3985 reflections with $I > 2\sigma(I)$
$R_{\rm int} = 0.026$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.031$
$wR(F^2) = 0.067$
$S = 1.06$
4327 reflections
227 parameters
1 restraint
H-atom parameters constrained
$\Delta\rho_{\max} = 0.34$ e Å^{-3}
$\Delta\rho_{\min} = -0.29$ e Å^{-3}
Absolute structure: Flack (1983), with 1887 Friedel pairs
Flack parameter: −0.020 (8)

All H atoms were initially located in electron-density difference maps. For all three compounds, C-bonded H atoms were constrained to idealized positions, with C—H = 0.95–1.00 Å and $U_{\rm iso}$(H) = $1.2U_{\rm eq}$(C). The hydroxy H atoms of (I) and (III) were also constrained to idealized positions, with O—H = 0.84 Å and $U_{\rm iso}$(H) = $1.5U_{\rm eq}$(O). For (II), the hydroxy H atom was freely refined.

For all compounds, data collection: *CrysAlis PRO* (Agilent, 2011); cell refinement: *CrysAlis PRO*; data reduction: *CrysAlis PRO*; program(s) used to solve structure: *SHELXD* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *OLEX2* (Dolomanov *et al.*, 2009); software used to prepare material for publication: *SHELXL97*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GZ3222). Services for accessing these data are described at the back of the journal.

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supplementary materials

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Relative configuration, absolute configuration and absolute structure of three isomeric 8-benzyl-2-[(4-bromophenyl)(hydroxy)methyl]-8-azabicyclo-[3.2.1]octan-3-ones

Krzysztof Brzezinski, Ryszard Lazny, Aneta Nodzewska and Katarzyna Sidorowicz

(I) (±)-*exo*,*syn*-(1*RS*,2*SR*,5*SR*)-8-Benzyl-2- [(*SR*)-(4-bromophenyl)(hydroxy)methyl]-8-azabicyclo[3.2.1]octan-3-one

Crystal data

$C_{21}H_{22}BrNO_2$
$M_r = 400.31$
Trigonal, $R\overline{3}$
Hall symbol: -R 3
$a = 29.8145$ (5) Å
$c = 10.2028$ (2) Å
$V = 7854.2$ (4) Å^3
$Z = 18$
$F(000) = 3708$
$D_x = 1.523$ Mg m^{-3}
Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
Cell parameters from 11027 reflections
$\theta = 2.7$–$29.5°$
$\mu = 2.36$ mm^{-1}
$T = 100$ K
Prism, colourless
0.54 × 0.46 × 0.29 mm

Data collection

Agilent SuperNova Dual diffractometer (Cu at zero) with Atlas detector
Radiation source: SuperNova (Mo) X-ray Source
Mirror monochromator
Detector resolution: 10.4052 pixels mm^{-1}
ω scans
Absorption correction: analytical (*CrysAlis PRO*; Agilent, 2011)
$T_{min} = 0.434$, $T_{max} = 0.633$
24029 measured reflections
4885 independent reflections
4130 reflections with $I > 2\sigma(I)$
$R_{int} = 0.033$
$\theta_{max} = 29.6°$, $\theta_{min} = 2.7°$
$h = -41 \rightarrow 38$
$k = -41 \rightarrow 40$
$l = -14 \rightarrow 12$

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)] = 0.033$
$wR(F^2) = 0.081$
$S = 1.06$
4885 reflections
227 parameters
0 restraints
Primary atom site location: structure-invariant direct methods
Secondary atom site location: difference Fourier map
Hydrogen site location: inferred from neighbouring sites
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0333P)^2 + 18.6115P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.004$
$\Delta\rho_{max} = 0.52$ e Å^{-3}
$\Delta\rho_{min} = -0.66$ e Å^{-3}

Special details

Geometry. All e.s.d.'s (except the e.s.d. in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell e.s.d.'s are taken into account individually in the estimation of e.s.d.'s in distances, angles and torsion angles; correlations between e.s.d.'s in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell e.s.d.'s is used for estimating e.s.d.'s involving l.s. planes.

Refinement. Refinement of F^2 against ALL reflections. The weighted R-factor wR and goodness of fit S are based on F^2, conventional R-factors R are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > \sigma(F^2)$ is used only for calculating R-factors(gt) *etc*. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

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

	x	y	z	$U_{\rm iso}$*/$U_{\rm eq}$
C1	0.16570 (6)	0.94796 (6)	0.71283 (16)	0.0114 (3)
H1	0.1709	0.9633	0.6231	0.014*
C2	0.10840 (6)	0.90755 (6)	0.73507 (16)	0.0123 (3)
H2	0.0886	0.9264	0.7428	0.015*
C3	0.10052 (7)	0.87706 (7)	0.86202 (18)	0.0165 (3)
C4	0.14678 (7)	0.87775 (7)	0.92536 (17)	0.0157 (3)
H4A	0.1439	0.8435	0.9117	0.019*
H4B	0.1453	0.8826	1.0210	0.019*
C5	0.19969 (7)	0.91966 (6)	0.87456 (17)	0.0137 (3)
H5	0.2274	0.9120	0.9013	0.016*
C6	0.21288 (7)	0.97402 (7)	0.92092 (17)	0.0162 (3)
H6A	0.2508	0.9979	0.9215	0.019*
H6B	0.1991	0.9727	1.0099	0.019*
C7	0.18603 (7)	0.99099 (6)	0.81840 (17)	0.0153 (3)
H7A	0.1571	0.9935	0.8587	0.018*
H7B	0.2110	1.0250	0.7800	0.018*
C9	0.08391 (6)	0.86743 (6)	0.62219 (17)	0.0135 (3)
H9C	0.0478	0.8418	0.6496	0.016*
C10	0.07998 (6)	0.89204 (6)	0.49583 (17)	0.0130 (3)
C11	0.03816 (6)	0.90032 (7)	0.47817 (18)	0.0157 (3)
H11	0.0122	0.8891	0.5439	0.019*
C12	0.03378 (7)	0.92454 (7)	0.36686 (19)	0.0171 (3)
H12	0.0052	0.9300	0.3563	0.021*
C13	0.07184 (7)	0.94069 (7)	0.27109 (17)	0.0164 (3)
C14	0.11339 (7)	0.93221 (7)	0.28452 (18)	0.0162 (3)
H14	0.1390	0.9430	0.2179	0.019*
C15	0.11708 (6)	0.90772 (6)	0.39687 (17)	0.0148 (3)
H15	0.1453	0.9016	0.4062	0.018*
C16	0.24871 (6)	0.95065 (7)	0.66966 (17)	0.0151 (3)
H16A	0.2712	0.9379	0.7052	0.018*
H16B	0.2643	0.9877	0.6935	0.018*
C17	0.24634 (6)	0.94546 (6)	0.52295 (17)	0.0129 (3)
C18	0.23544 (6)	0.89856 (7)	0.46486 (18)	0.0144 (3)
H18	0.2302	0.8704	0.5188	0.017*
C19	0.23212 (7)	0.89259 (7)	0.33004 (18)	0.0167 (3)
H19	0.2243	0.8604	0.2920	0.020*
C20	0.24027 (7)	0.93395 (7)	0.25023 (18)	0.0170 (3)

H20	0.2382	0.9300	0.1576	0.020*
C21	0.25148 (7)	0.98090 (7)	0.30617 (18)	0.0173 (3)
H21	0.2572	1.0092	0.2519	0.021*
C22	0.25429 (6)	0.98643 (6)	0.44173 (18)	0.0151 (3)
H22	0.2617	1.0185	0.4795	0.018*
N8	0.19619 (5)	0.92084 (5)	0.72953 (14)	0.0118 (3)
O3	0.05746 (6)	0.85040 (6)	0.90646 (15)	0.0310 (3)
O9	0.11078 (5)	0.83943 (5)	0.60591 (13)	0.0162 (3)
H9O	0.1418	0.8582	0.6286	0.024*
Br13	0.068838 (8)	0.977249 (8)	0.12272 (2)	0.02544 (7)

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
C1	0.0141 (7)	0.0100 (7)	0.0104 (8)	0.0063 (6)	0.0004 (6)	0.0007 (6)
C2	0.0143 (7)	0.0116 (7)	0.0112 (8)	0.0068 (6)	0.0018 (6)	0.0004 (6)
C3	0.0211 (8)	0.0157 (8)	0.0132 (8)	0.0095 (7)	0.0042 (6)	0.0019 (6)
C4	0.0234 (9)	0.0139 (8)	0.0113 (8)	0.0104 (7)	0.0029 (6)	0.0025 (6)
C5	0.0187 (8)	0.0146 (7)	0.0095 (8)	0.0096 (7)	−0.0011 (6)	0.0005 (6)
C6	0.0226 (8)	0.0141 (8)	0.0119 (8)	0.0092 (7)	−0.0020 (6)	−0.0025 (6)
C7	0.0208 (8)	0.0115 (7)	0.0142 (8)	0.0086 (7)	−0.0022 (6)	−0.0013 (6)
C9	0.0130 (7)	0.0113 (7)	0.0149 (8)	0.0052 (6)	0.0019 (6)	0.0001 (6)
C10	0.0116 (7)	0.0099 (7)	0.0146 (8)	0.0032 (6)	−0.0012 (6)	−0.0027 (6)
C11	0.0106 (7)	0.0156 (8)	0.0183 (9)	0.0046 (6)	0.0000 (6)	−0.0016 (6)
C12	0.0121 (7)	0.0158 (8)	0.0215 (9)	0.0056 (6)	−0.0043 (7)	−0.0023 (7)
C13	0.0181 (8)	0.0143 (8)	0.0131 (8)	0.0054 (7)	−0.0055 (6)	−0.0015 (6)
C14	0.0148 (8)	0.0169 (8)	0.0135 (8)	0.0054 (6)	−0.0001 (6)	−0.0029 (6)
C15	0.0127 (7)	0.0151 (8)	0.0158 (8)	0.0065 (6)	−0.0006 (6)	−0.0031 (6)
C16	0.0113 (7)	0.0200 (8)	0.0134 (8)	0.0074 (6)	0.0001 (6)	−0.0020 (6)
C17	0.0093 (7)	0.0158 (7)	0.0131 (8)	0.0058 (6)	0.0016 (6)	0.0002 (6)
C18	0.0129 (7)	0.0145 (7)	0.0162 (9)	0.0072 (6)	0.0026 (6)	0.0016 (6)
C19	0.0155 (8)	0.0177 (8)	0.0179 (9)	0.0092 (7)	0.0018 (6)	−0.0040 (7)
C20	0.0153 (8)	0.0259 (9)	0.0118 (8)	0.0118 (7)	0.0004 (6)	−0.0015 (7)
C21	0.0171 (8)	0.0203 (8)	0.0156 (9)	0.0102 (7)	0.0019 (6)	0.0049 (7)
C22	0.0125 (7)	0.0130 (7)	0.0184 (9)	0.0052 (6)	0.0008 (6)	−0.0007 (6)
N8	0.0133 (6)	0.0128 (6)	0.0103 (7)	0.0073 (5)	0.0011 (5)	0.0008 (5)
O3	0.0223 (7)	0.0379 (8)	0.0273 (8)	0.0111 (7)	0.0108 (6)	0.0166 (7)
O9	0.0169 (6)	0.0127 (6)	0.0203 (7)	0.0084 (5)	−0.0024 (5)	−0.0027 (5)
Br13	0.02526 (11)	0.02610 (11)	0.02010 (11)	0.00920 (8)	−0.00645 (7)	0.00505 (7)

Geometric parameters (Å, º)

C1—N8	1.498 (2)	C11—C12	1.386 (3)
C1—C2	1.537 (2)	C11—H11	0.9500
C1—C7	1.548 (2)	C12—C13	1.388 (3)
C1—H1	1.0000	C12—H12	0.9500
C2—C3	1.531 (2)	C13—C14	1.390 (2)
C2—C9	1.555 (2)	C13—Br13	1.8935 (18)
C2—H2	1.0000	C14—C15	1.393 (2)
C3—O3	1.210 (2)	C14—H14	0.9500

C3—C4	1.514 (3)	C15—H15	0.9500
C4—C5	1.532 (2)	C16—N8	1.491 (2)
C4—H4A	0.9900	C16—C17	1.503 (2)
C4—H4B	0.9900	C16—H16A	0.9900
C5—N8	1.485 (2)	C16—H16B	0.9900
C5—C6	1.539 (2)	C17—C22	1.395 (2)
C5—H5	1.0000	C17—C18	1.399 (2)
C6—C7	1.548 (2)	C18—C19	1.384 (3)
C6—H6A	0.9900	C18—H18	0.9500
C6—H6B	0.9900	C19—C20	1.394 (3)
C7—H7A	0.9900	C19—H19	0.9500
C7—H7B	0.9900	C20—C21	1.389 (3)
C9—O9	1.426 (2)	C20—H20	0.9500
C9—C10	1.517 (2)	C21—C22	1.391 (3)
C9—H9C	1.0000	C21—H21	0.9500
C10—C15	1.395 (2)	C22—H22	0.9500
C10—C11	1.399 (2)	O9—H9O	0.8400

N8—C1—C2	107.26 (12)	C15—C10—C9	122.51 (15)
N8—C1—C7	106.04 (13)	C11—C10—C9	119.10 (15)
C2—C1—C7	111.59 (13)	C12—C11—C10	121.46 (16)
N8—C1—H1	110.6	C12—C11—H11	119.3
C2—C1—H1	110.6	C10—C11—H11	119.3
C7—C1—H1	110.6	C13—C12—C11	118.93 (16)
C3—C2—C1	111.76 (14)	C13—C12—H12	120.5
C3—C2—C9	107.23 (13)	C11—C12—H12	120.5
C1—C2—C9	113.83 (13)	C12—C13—C14	121.06 (16)
C3—C2—H2	107.9	C12—C13—Br13	119.78 (13)
C1—C2—H2	107.9	C14—C13—Br13	119.12 (14)
C9—C2—H2	107.9	C13—C14—C15	119.21 (16)
O3—C3—C4	120.59 (16)	C13—C14—H14	120.4
O3—C3—C2	120.29 (17)	C15—C14—H14	120.4
C4—C3—C2	118.98 (15)	C14—C15—C10	120.95 (16)
C3—C4—C5	115.22 (14)	C14—C15—H15	119.5
C3—C4—H4A	108.5	C10—C15—H15	119.5
C5—C4—H4A	108.5	N8—C16—C17	111.44 (14)
C3—C4—H4B	108.5	N8—C16—H16A	109.3
C5—C4—H4B	108.5	C17—C16—H16A	109.3
H4A—C4—H4B	107.5	N8—C16—H16B	109.3
N8—C5—C4	107.49 (14)	C17—C16—H16B	109.3
N8—C5—C6	105.39 (13)	H16A—C16—H16B	108.0
C4—C5—C6	111.83 (14)	C22—C17—C18	118.45 (16)
N8—C5—H5	110.7	C22—C17—C16	121.52 (15)
C4—C5—H5	110.7	C18—C17—C16	120.02 (15)
C6—C5—H5	110.7	C19—C18—C17	121.02 (16)
C5—C6—C7	103.59 (13)	C19—C18—H18	119.5
C5—C6—H6A	111.0	C17—C18—H18	119.5
C7—C6—H6A	111.0	C18—C19—C20	119.81 (16)
C5—C6—H6B	111.0	C18—C19—H19	120.1

C7—C6—H6B	111.0	C20—C19—H19	120.1
H6A—C6—H6B	109.0	C21—C20—C19	119.95 (16)
C1—C7—C6	104.57 (13)	C21—C20—H20	120.0
C1—C7—H7A	110.8	C19—C20—H20	120.0
C6—C7—H7A	110.8	C20—C21—C22	119.88 (16)
C1—C7—H7B	110.8	C20—C21—H21	120.1
C6—C7—H7B	110.8	C22—C21—H21	120.1
H7A—C7—H7B	108.9	C21—C22—C17	120.88 (16)
O9—C9—C10	112.70 (14)	C21—C22—H22	119.6
O9—C9—C2	110.56 (13)	C17—C22—H22	119.6
C10—C9—C2	112.19 (13)	C5—N8—C16	110.92 (13)
O9—C9—H9C	107.0	C5—N8—C1	101.24 (12)
C10—C9—H9C	107.0	C16—N8—C1	111.80 (13)
C2—C9—H9C	107.0	C9—O9—H9O	109.5
C15—C10—C11	118.38 (16)		

(II) (+)-*exo,anti*-(1*R*,2*S*,5*S*)-8-Benzyl- 2-[(*R*)-(4-bromophenyl)(hydroxy)methyl]-8-azabicyclo[3.2.1]octan-3-one

Crystal data

$C_{21}H_{22}BrNO_2$
$M_r = 400.31$
Orthorhombic, $P2_12_12_1$
Hall symbol: P 2ac 2ab
$a = 5.96905$ (4) Å
$b = 14.76590$ (9) Å
$c = 20.76083$ (13) Å
$V = 1829.83$ (2) Å^3
$Z = 4$

$F(000) = 824$
$D_x = 1.453$ Mg m^{-3}
Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
Cell parameters from 28586 reflections
$\theta = 2.8$–31.7°
$\mu = 2.26$ mm^{-1}
$T = 100$ K
Needle, colourless
0.52 × 0.11 × 0.09 mm

Data collection

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Radiation source: SuperNova (Mo) X-ray Source
Mirror monochromator
Detector resolution: 10.4052 pixels mm^{-1}
ω scans
Absorption correction: analytical (*CrysAlis PRO*; Agilent, 2011)

$T_{min} = 0.308$, $T_{max} = 0.816$
67899 measured reflections
5359 independent reflections
5007 reflections with $I > 2\sigma(I)$
$R_{int} = 0.064$
$\theta_{max} = 30.0°$, $\theta_{min} = 2.8°$
$h = -8\rightarrow 8$
$k = 0\rightarrow 20$
$l = 0\rightarrow 29$

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)] = 0.033$
$wR(F^2) = 0.080$
$S = 1.04$
5359 reflections
230 parameters
0 restraints
Primary atom site location: structure-invariant direct methods
Secondary atom site location: difference Fourier map

Hydrogen site location: inferred from neighbouring sites
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0364P)^2 + 1.3126P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.002$
$\Delta\rho_{max} = 0.64$ e Å^{-3}
$\Delta\rho_{min} = -0.48$ e Å^{-3}
Absolute structure: Flack (1983), with 2292 Friedel pairs
Flack parameter: −0.011 (7)

Special details

Geometry. All e.s.d.'s (except the e.s.d. in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell e.s.d.'s are taken into account individually in the estimation of e.s.d.'s in distances, angles and torsion angles; correlations between e.s.d.'s in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell e.s.d.'s is used for estimating e.s.d.'s involving l.s. planes.

Refinement. Refinement of F^2 against ALL reflections. The weighted *R*-factor *wR* and goodness of fit *S* are based on F^2, conventional *R*-factors *R* are based on *F*, with *F* set to zero for negative F^2. The threshold expression of $F^2 > \sigma(F^2)$ is used only for calculating *R*-factors(gt) *etc*. and is not relevant to the choice of reflections for refinement. *R*-factors based on F^2 are statistically about twice as large as those based on *F*, and *R*-factors based on ALL data will be even larger.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²)

	x	*y*	*z*	U_{iso}*/U_{eq}
C1	0.1312 (3)	0.55838 (13)	0.31042 (9)	0.0135 (3)
H1	0.0970	0.5167	0.3471	0.016*
C2	0.1759 (3)	0.65521 (13)	0.33494 (9)	0.0137 (3)
H2	0.0353	0.6776	0.3557	0.016*
C3	0.2284 (3)	0.71768 (14)	0.27886 (9)	0.0152 (4)
C4	0.3650 (4)	0.67675 (14)	0.22454 (10)	0.0184 (4)
H4A	0.5263	0.6827	0.2349	0.022*
H4B	0.3362	0.7112	0.1845	0.022*
C5	0.3101 (4)	0.57637 (14)	0.21296 (9)	0.0160 (4)
H5	0.4103	0.5499	0.1793	0.019*
C6	0.0607 (4)	0.56476 (15)	0.19451 (10)	0.0200 (4)
H6A	0.0056	0.6179	0.1701	0.024*
H6B	0.0382	0.5096	0.1682	0.024*
C7	−0.0594 (3)	0.55655 (15)	0.25996 (10)	0.0201 (4)
H7A	−0.1447	0.4991	0.2626	0.024*
H7B	−0.1638	0.6078	0.2666	0.024*
C9	0.3654 (3)	0.65803 (13)	0.38653 (9)	0.0143 (4)
H9C	0.3154	0.6208	0.4241	0.017*
C10	0.4132 (4)	0.75302 (12)	0.41086 (9)	0.0138 (3)
C11	0.2675 (4)	0.79506 (14)	0.45369 (10)	0.0180 (4)
H11	0.1325	0.7654	0.4656	0.022*
C12	0.3161 (4)	0.88017 (15)	0.47949 (10)	0.0212 (4)
H12	0.2161	0.9086	0.5088	0.025*
C13	0.5142 (4)	0.92214 (14)	0.46127 (10)	0.0181 (4)
C14	0.6610 (4)	0.88237 (14)	0.41832 (10)	0.0185 (4)
H14	0.7953	0.9124	0.4063	0.022*
C15	0.6091 (4)	0.79761 (13)	0.39295 (9)	0.0165 (4)
H15	0.7084	0.7699	0.3631	0.020*
C16	0.3379 (3)	0.42820 (13)	0.26515 (9)	0.0153 (4)
H16A	0.4640	0.4123	0.2363	0.018*
H16B	0.1972	0.4094	0.2438	0.018*
C17	0.3623 (3)	0.37737 (13)	0.32782 (9)	0.0141 (4)
C18	0.5521 (3)	0.38911 (14)	0.36635 (10)	0.0169 (4)
H18	0.6643	0.4312	0.3538	0.020*
C19	0.5780 (4)	0.33984 (14)	0.42264 (10)	0.0203 (4)
H19	0.7069	0.3487	0.4487	0.024*
C20	0.4160 (4)	0.27755 (14)	0.44106 (9)	0.0209 (4)

H20	0.4351	0.2431	0.4793	0.025*
C21	0.2259 (4)	0.26583 (14)	0.40347 (10)	0.0199 (4)
H21	0.1147	0.2233	0.4160	0.024*
C22	0.1982 (4)	0.31643 (14)	0.34735 (9)	0.0165 (4)
H22	0.0663	0.3092	0.3223	0.020*
N8	0.3346 (3)	0.52773 (11)	0.27504 (7)	0.0127 (3)
O3	0.1665 (3)	0.79597 (10)	0.27787 (7)	0.0223 (3)
O9	0.5686 (3)	0.62051 (10)	0.36339 (7)	0.0188 (3)
H9O	0.529 (6)	0.584 (2)	0.3352 (17)	0.049 (10)*
Br13	0.59443 (4)	1.035874 (13)	0.497759 (12)	0.02729 (7)

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
C1	0.0134 (9)	0.0133 (8)	0.0138 (8)	−0.0004 (7)	0.0020 (6)	−0.0001 (6)
C2	0.0121 (8)	0.0143 (9)	0.0146 (8)	0.0015 (7)	0.0007 (7)	0.0000 (7)
C3	0.0151 (9)	0.0138 (9)	0.0167 (9)	0.0005 (7)	−0.0036 (7)	0.0024 (7)
C4	0.0220 (10)	0.0146 (9)	0.0187 (9)	0.0021 (7)	0.0035 (8)	0.0059 (7)
C5	0.0197 (9)	0.0149 (9)	0.0134 (8)	0.0044 (7)	0.0021 (7)	0.0039 (7)
C6	0.0236 (11)	0.0207 (10)	0.0155 (9)	0.0039 (8)	−0.0047 (8)	0.0008 (7)
C7	0.0148 (9)	0.0244 (11)	0.0211 (9)	0.0016 (8)	−0.0014 (7)	−0.0039 (8)
C9	0.0169 (9)	0.0129 (8)	0.0132 (8)	0.0013 (7)	−0.0006 (7)	0.0006 (6)
C10	0.0171 (9)	0.0126 (8)	0.0118 (8)	0.0025 (8)	−0.0015 (7)	0.0009 (6)
C11	0.0179 (9)	0.0194 (10)	0.0166 (9)	−0.0005 (8)	0.0026 (7)	−0.0016 (7)
C12	0.0246 (10)	0.0199 (10)	0.0191 (9)	0.0039 (8)	0.0015 (8)	−0.0050 (7)
C13	0.0256 (10)	0.0110 (9)	0.0177 (9)	0.0020 (8)	−0.0027 (8)	−0.0012 (7)
C14	0.0210 (10)	0.0156 (9)	0.0189 (9)	−0.0018 (8)	0.0012 (7)	0.0041 (7)
C15	0.0168 (9)	0.0165 (9)	0.0161 (8)	0.0020 (8)	0.0034 (7)	0.0008 (7)
C16	0.0196 (9)	0.0124 (8)	0.0138 (8)	0.0011 (7)	−0.0011 (7)	−0.0006 (6)
C17	0.0172 (9)	0.0107 (8)	0.0142 (8)	0.0016 (7)	−0.0004 (7)	−0.0011 (6)
C18	0.0171 (10)	0.0129 (8)	0.0207 (9)	−0.0001 (7)	−0.0021 (7)	0.0005 (7)
C19	0.0245 (10)	0.0170 (9)	0.0193 (9)	0.0000 (9)	−0.0064 (8)	0.0010 (7)
C20	0.0322 (11)	0.0147 (9)	0.0157 (8)	0.0001 (9)	−0.0006 (9)	0.0019 (7)
C21	0.0274 (11)	0.0145 (9)	0.0177 (9)	−0.0057 (8)	0.0039 (8)	−0.0014 (7)
C22	0.0173 (9)	0.0157 (9)	0.0164 (9)	−0.0017 (8)	−0.0001 (7)	−0.0037 (7)
N8	0.0141 (7)	0.0114 (7)	0.0127 (7)	0.0014 (6)	0.0018 (5)	0.0019 (6)
O3	0.0303 (8)	0.0136 (7)	0.0229 (7)	0.0059 (6)	−0.0067 (6)	0.0007 (6)
O9	0.0155 (7)	0.0167 (7)	0.0241 (7)	0.0053 (6)	−0.0034 (6)	−0.0063 (6)
Br13	0.03686 (12)	0.01334 (9)	0.03168 (11)	0.00017 (8)	−0.00484 (11)	−0.00574 (9)

Geometric parameters (Å, º)

C1—N8	1.489 (2)	C11—C12	1.397 (3)
C1—C2	1.541 (3)	C11—H11	0.9500
C1—C7	1.547 (3)	C12—C13	1.387 (3)
C1—H1	1.0000	C12—H12	0.9500
C2—C3	1.518 (3)	C13—C14	1.381 (3)
C2—C9	1.558 (3)	C13—Br13	1.904 (2)
C2—H2	1.0000	C14—C15	1.393 (3)
C3—O3	1.214 (3)	C14—H14	0.9500

C3—C4	1.517 (3)	C15—H15	0.9500
C4—C5	1.537 (3)	C16—N8	1.484 (3)
C4—H4A	0.9900	C16—C17	1.509 (3)
C4—H4B	0.9900	C16—H16A	0.9900
C5—N8	1.483 (2)	C16—H16B	0.9900
C5—C6	1.547 (3)	C17—C22	1.391 (3)
C5—H5	1.0000	C17—C18	1.398 (3)
C6—C7	1.541 (3)	C18—C19	1.385 (3)
C6—H6A	0.9900	C18—H18	0.9500
C6—H6B	0.9900	C19—C20	1.388 (3)
C7—H7A	0.9900	C19—H19	0.9500
C7—H7B	0.9900	C20—C21	1.388 (3)
C9—O9	1.417 (2)	C20—H20	0.9500
C9—C10	1.518 (3)	C21—C22	1.394 (3)
C9—H9C	1.0000	C21—H21	0.9500
C10—C11	1.390 (3)	C22—H22	0.9500
C10—C15	1.393 (3)	O9—H9O	0.83 (4)

N8—C1—C2	107.67 (15)	C11—C10—C9	120.53 (19)
N8—C1—C7	105.08 (15)	C15—C10—C9	120.38 (17)
C2—C1—C7	111.55 (16)	C10—C11—C12	121.1 (2)
N8—C1—H1	110.8	C10—C11—H11	119.4
C2—C1—H1	110.8	C12—C11—H11	119.4
C7—C1—H1	110.8	C13—C12—C11	118.32 (19)
C3—C2—C1	110.26 (15)	C13—C12—H12	120.8
C3—C2—C9	111.16 (16)	C11—C12—H12	120.8
C1—C2—C9	112.18 (15)	C14—C13—C12	121.78 (19)
C3—C2—H2	107.7	C14—C13—Br13	118.19 (17)
C1—C2—H2	107.7	C12—C13—Br13	120.00 (16)
C9—C2—H2	107.7	C13—C14—C15	119.0 (2)
O3—C3—C4	122.03 (18)	C13—C14—H14	120.5
O3—C3—C2	121.93 (18)	C15—C14—H14	120.5
C4—C3—C2	116.04 (16)	C14—C15—C10	120.70 (19)
C3—C4—C5	112.68 (17)	C14—C15—H15	119.7
C3—C4—H4A	109.1	C10—C15—H15	119.7
C5—C4—H4A	109.1	N8—C16—C17	111.99 (16)
C3—C4—H4B	109.1	N8—C16—H16A	109.2
C5—C4—H4B	109.1	C17—C16—H16A	109.2
H4A—C4—H4B	107.8	N8—C16—H16B	109.2
N8—C5—C4	108.07 (16)	C17—C16—H16B	109.2
N8—C5—C6	104.87 (16)	H16A—C16—H16B	107.9
C4—C5—C6	110.56 (17)	C22—C17—C18	118.98 (18)
N8—C5—H5	111.0	C22—C17—C16	120.33 (18)
C4—C5—H5	111.0	C18—C17—C16	120.67 (18)
C6—C5—H5	111.0	C19—C18—C17	120.53 (19)
C7—C6—C5	103.78 (16)	C19—C18—H18	119.7
C7—C6—H6A	111.0	C17—C18—H18	119.7
C5—C6—H6A	111.0	C18—C19—C20	120.2 (2)
C7—C6—H6B	111.0	C18—C19—H19	119.9

C5—C6—H6B	111.0	C20—C19—H19	119.9
H6A—C6—H6B	109.0	C21—C20—C19	119.81 (19)
C6—C7—C1	104.69 (16)	C21—C20—H20	120.1
C6—C7—H7A	110.8	C19—C20—H20	120.1
C1—C7—H7A	110.8	C20—C21—C22	120.0 (2)
C6—C7—H7B	110.8	C20—C21—H21	120.0
C1—C7—H7B	110.8	C22—C21—H21	120.0
H7A—C7—H7B	108.9	C17—C22—C21	120.46 (19)
O9—C9—C10	108.26 (16)	C17—C22—H22	119.8
O9—C9—C2	112.21 (15)	C21—C22—H22	119.8
C10—C9—C2	112.93 (16)	C5—N8—C16	111.15 (15)
O9—C9—H9C	107.7	C5—N8—C1	101.60 (14)
C10—C9—H9C	107.7	C16—N8—C1	112.33 (15)
C2—C9—H9C	107.7	C9—O9—H9O	105 (3)
C11—C10—C15	119.02 (18)		

(III) (±)-*exo,anti*-(1*RS*,2*SR*,5*SR*)-8-Benzyl-2- [(*RS*)-(4-bromophenyl)(hydroxy)methyl]-8-azabicyclo[3.2.1]octan-3-one

Crystal data

$C_{21}H_{22}BrNO_2$
$M_r = 400.31$
Orthorhombic, $Pna2_1$
Hall symbol: P 2c -2n
$a = 9.0968\ (4)$ Å
$b = 32.0680\ (18)$ Å
$c = 6.1711\ (4)$ Å
$V = 1800.22\ (17)$ Å^3
$Z = 4$

$F(000) = 824$
$D_x = 1.477$ Mg m^{-3}
Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
Cell parameters from 10458 reflections
$\theta = 2.9–28.2°$
$\mu = 2.30$ mm^{-1}
$T = 100$ K
Needle, colourless
0.80 × 0.09 × 0.07 mm

Data collection

Agilent SuperNova Dual diffractometer (Cu at zero) with Atlas detector
Radiation source: SuperNova (Mo) X-ray Source
Mirror monochromator
Detector resolution: 10.4052 pixels mm^{-1}
ω scans
Absorption correction: analytical (*CrysAlis PRO*; Agilent, 2011)

$T_{min} = 0.726$, $T_{max} = 0.870$
9954 measured reflections
4327 independent reflections
3985 reflections with $I > 2\sigma(I)$
$R_{int} = 0.026$
$\theta_{max} = 28.3°$, $\theta_{min} = 2.9°$
$h = -11 \rightarrow 12$
$k = -42 \rightarrow 42$
$l = -7 \rightarrow 8$

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)] = 0.031$
$wR(F^2) = 0.067$
$S = 1.06$
4327 reflections
227 parameters
1 restraint
Primary atom site location: structure-invariant direct methods
Secondary atom site location: difference Fourier map

Hydrogen site location: inferred from neighbouring sites
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0278P)^2 + 0.5747P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.002$
$\Delta\rho_{max} = 0.34$ e Å^{-3}
$\Delta\rho_{min} = -0.29$ e Å^{-3}
Absolute structure: Flack (1983), with 1887 Friedel pairs
Flack parameter: −0.020 (8)

Special details

Geometry. All e.s.d.'s (except the e.s.d. in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell e.s.d.'s are taken into account individually in the estimation of e.s.d.'s in distances, angles and torsion angles; correlations between e.s.d.'s in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell e.s.d.'s is used for estimating e.s.d.'s involving l.s. planes.

Refinement. Refinement of F^2 against ALL reflections. The weighted *R*-factor *wR* and goodness of fit *S* are based on F^2, conventional *R*-factors *R* are based on *F*, with *F* set to zero for negative F^2. The threshold expression of $F^2 > \sigma(F^2)$ is used only for calculating *R*-factors(gt) *etc*. and is not relevant to the choice of reflections for refinement. *R*-factors based on F^2 are statistically about twice as large as those based on *F*, and *R*-factors based on ALL data will be even larger.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters ($\AA^2$)

	x	*y*	*z*	$U_{\rm iso}$*/$U_{\rm eq}$
C1	0.7396 (3)	0.40451 (7)	0.6389 (4)	0.0152 (5)
H1	0.7933	0.3789	0.6859	0.018*
C2	0.8347 (2)	0.44367 (7)	0.6741 (4)	0.0147 (5)
H2	0.8580	0.4458	0.8320	0.018*
C3	0.7443 (3)	0.48150 (7)	0.6102 (4)	0.0174 (5)
C4	0.6577 (3)	0.47719 (8)	0.4042 (4)	0.0189 (5)
H4A	0.7241	0.4807	0.2784	0.023*
H4B	0.5821	0.4994	0.3975	0.023*
C5	0.5825 (3)	0.43415 (7)	0.3920 (4)	0.0188 (5)
H5	0.5254	0.4312	0.2544	0.023*
C6	0.4833 (3)	0.42654 (8)	0.5910 (4)	0.0189 (5)
H6A	0.4046	0.4062	0.5574	0.023*
H6B	0.4379	0.4529	0.6417	0.023*
C7	0.5914 (3)	0.40887 (8)	0.7622 (4)	0.0207 (5)
H7A	0.6013	0.4282	0.8864	0.025*
H7B	0.5574	0.3815	0.8163	0.025*
C9	0.9808 (2)	0.44178 (7)	0.5477 (4)	0.0150 (5)
H9A	0.9609	0.4347	0.3927	0.018*
C10	1.0798 (2)	0.40908 (7)	0.6471 (4)	0.0155 (5)
C11	1.1104 (2)	0.37206 (7)	0.5391 (4)	0.0175 (5)
H11	1.0710	0.3676	0.3984	0.021*
C12	1.1984 (3)	0.34127 (7)	0.6346 (4)	0.0208 (5)
H12	1.2192	0.3160	0.5602	0.025*
C13	1.2544 (3)	0.34845 (7)	0.8393 (4)	0.0185 (5)
C14	1.2264 (2)	0.38538 (6)	0.9508 (5)	0.0186 (5)
H14	1.2668	0.3900	1.0908	0.022*
C15	1.1385 (2)	0.41532 (7)	0.8534 (4)	0.0173 (5)
H15	1.1179	0.4405	0.9284	0.021*
C16	0.6393 (3)	0.36003 (8)	0.3520 (4)	0.0224 (5)
H16A	0.5833	0.3617	0.2147	0.027*
H16B	0.5710	0.3509	0.4676	0.027*
C17	0.7611 (3)	0.32839 (7)	0.3283 (4)	0.0199 (5)
C18	0.7944 (3)	0.29981 (6)	0.4914 (6)	0.0249 (5)
H18	0.7375	0.2995	0.6205	0.030*
C19	0.9101 (3)	0.27178 (6)	0.4670 (6)	0.0295 (6)
H19	0.9322	0.2526	0.5799	0.035*
C20	0.9931 (3)	0.27170 (8)	0.2789 (5)	0.0290 (6)

H20	1.0727	0.2528	0.2629	0.035*
C21	0.9590 (3)	0.29945 (8)	0.1140 (5)	0.0252 (6)
H21	1.0141	0.2992	−0.0168	0.030*
C22	0.8446 (3)	0.32758 (8)	0.1401 (4)	0.0213 (5)
H22	0.8230	0.3467	0.0269	0.026*
N8	0.6991 (2)	0.40193 (6)	0.4065 (3)	0.0158 (4)
O3	0.73771 (18)	0.51265 (5)	0.7239 (3)	0.0217 (4)
O9	1.04507 (18)	0.48249 (5)	0.5611 (3)	0.0197 (4)
H9O	1.1095	0.4851	0.4645	0.030*
Br13	1.36610 (2)	0.305844 (6)	0.97680 (7)	0.02681 (7)

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
C1	0.0177 (11)	0.0139 (10)	0.0140 (12)	−0.0016 (9)	−0.0008 (9)	0.0024 (10)
C2	0.0118 (10)	0.0151 (10)	0.0172 (12)	−0.0005 (8)	0.0004 (9)	0.0004 (9)
C3	0.0132 (11)	0.0158 (11)	0.0233 (14)	−0.0018 (9)	0.0044 (10)	0.0022 (10)
C4	0.0190 (12)	0.0192 (11)	0.0186 (13)	0.0041 (9)	0.0006 (9)	0.0042 (9)
C5	0.0158 (11)	0.0226 (11)	0.0180 (12)	0.0019 (10)	−0.0044 (9)	0.0005 (10)
C6	0.0164 (11)	0.0221 (12)	0.0181 (13)	−0.0010 (9)	0.0001 (10)	−0.0036 (10)
C7	0.0183 (12)	0.0266 (12)	0.0170 (13)	−0.0069 (10)	0.0026 (10)	0.0008 (10)
C9	0.0117 (10)	0.0154 (10)	0.0178 (12)	−0.0006 (9)	−0.0003 (9)	0.0001 (8)
C10	0.0111 (10)	0.0167 (11)	0.0186 (12)	−0.0030 (9)	0.0009 (9)	0.0008 (9)
C11	0.0164 (11)	0.0185 (10)	0.0176 (14)	−0.0019 (9)	−0.0019 (8)	−0.0021 (9)
C12	0.0177 (12)	0.0147 (11)	0.0299 (14)	0.0001 (9)	−0.0015 (10)	−0.0037 (10)
C13	0.0163 (11)	0.0137 (10)	0.0256 (13)	0.0008 (9)	−0.0035 (10)	0.0044 (10)
C14	0.0161 (9)	0.0214 (10)	0.0181 (14)	−0.0030 (8)	−0.0018 (11)	0.0008 (11)
C15	0.0145 (11)	0.0180 (11)	0.0193 (13)	−0.0004 (9)	0.0032 (10)	−0.0024 (10)
C16	0.0202 (12)	0.0233 (12)	0.0236 (14)	−0.0022 (10)	−0.0021 (10)	−0.0080 (11)
C17	0.0219 (12)	0.0167 (11)	0.0211 (13)	−0.0077 (9)	−0.0035 (10)	−0.0041 (10)
C18	0.0330 (12)	0.0223 (11)	0.0193 (13)	−0.0109 (9)	−0.0027 (14)	−0.0008 (14)
C19	0.0423 (14)	0.0152 (9)	0.0310 (14)	−0.0071 (9)	−0.0136 (18)	0.0041 (15)
C20	0.0273 (14)	0.0174 (11)	0.0424 (18)	0.0009 (11)	−0.0149 (13)	−0.0091 (12)
C21	0.0244 (13)	0.0241 (13)	0.0271 (15)	−0.0030 (10)	−0.0001 (11)	−0.0074 (11)
C22	0.0264 (13)	0.0196 (12)	0.0177 (13)	−0.0041 (10)	−0.0036 (10)	0.0004 (10)
N8	0.0156 (9)	0.0166 (9)	0.0151 (11)	0.0005 (8)	−0.0016 (8)	−0.0017 (8)
O3	0.0199 (9)	0.0172 (8)	0.0281 (10)	0.0011 (7)	−0.0003 (8)	−0.0033 (7)
O9	0.0193 (8)	0.0153 (7)	0.0245 (9)	−0.0035 (7)	0.0036 (7)	0.0021 (7)
Br13	0.02635 (12)	0.01963 (10)	0.03446 (14)	0.00432 (9)	−0.01027 (15)	0.00369 (15)

Geometric parameters (Å, º)

C1—N8	1.483 (3)	C11—C12	1.402 (3)
C1—C2	1.540 (3)	C11—H11	0.9500
C1—C7	1.555 (3)	C12—C13	1.382 (4)
C1—H1	1.0000	C12—H12	0.9500
C2—C3	1.518 (3)	C13—C14	1.393 (3)
C2—C9	1.542 (3)	C13—Br13	1.902 (2)
C2—H2	1.0000	C14—C15	1.387 (3)
C3—O3	1.222 (3)	C14—H14	0.9500

C3—C4	1.502 (3)	C15—H15	0.9500
C4—C5	1.542 (3)	C16—N8	1.488 (3)
C4—H4A	0.9900	C16—C17	1.509 (3)
C4—H4B	0.9900	C16—H16A	0.9900
C5—N8	1.483 (3)	C16—H16B	0.9900
C5—C6	1.544 (3)	C17—C18	1.394 (4)
C5—H5	1.0000	C17—C22	1.388 (4)
C6—C7	1.551 (3)	C18—C19	1.392 (3)
C6—H6A	0.9900	C18—H18	0.9500
C6—H6B	0.9900	C19—C20	1.385 (5)
C7—H7A	0.9900	C19—H19	0.9500
C7—H7B	0.9900	C20—C21	1.387 (4)
C9—O9	1.433 (3)	C20—H20	0.9500
C9—C10	1.512 (3)	C21—C22	1.386 (4)
C9—H9A	1.0000	C21—H21	0.9500
C10—C11	1.389 (3)	C22—H22	0.9500
C10—C15	1.395 (4)	O9—H9O	0.8400

N8—C1—C2	108.8 (2)	C11—C10—C9	121.1 (2)
N8—C1—C7	105.24 (18)	C15—C10—C9	119.9 (2)
C2—C1—C7	110.17 (19)	C10—C11—C12	121.0 (2)
N8—C1—H1	110.8	C10—C11—H11	119.5
C2—C1—H1	110.8	C12—C11—H11	119.5
C7—C1—H1	110.8	C13—C12—C11	118.5 (2)
C3—C2—C1	108.12 (19)	C13—C12—H12	120.7
C3—C2—C9	111.52 (19)	C11—C12—H12	120.7
C1—C2—C9	112.37 (19)	C12—C13—C14	121.7 (2)
C3—C2—H2	108.2	C12—C13—Br13	119.02 (18)
C1—C2—H2	108.2	C14—C13—Br13	119.19 (19)
C9—C2—H2	108.2	C15—C14—C13	118.7 (2)
O3—C3—C4	122.4 (2)	C15—C14—H14	120.7
O3—C3—C2	122.1 (2)	C13—C14—H14	120.7
C4—C3—C2	115.5 (2)	C14—C15—C10	121.1 (2)
C3—C4—C5	110.87 (19)	C14—C15—H15	119.4
C3—C4—H4A	109.5	C10—C15—H15	119.4
C5—C4—H4A	109.5	N8—C16—C17	111.14 (19)
C3—C4—H4B	109.5	N8—C16—H16A	109.4
C5—C4—H4B	109.5	C17—C16—H16A	109.4
H4A—C4—H4B	108.1	N8—C16—H16B	109.4
N8—C5—C4	107.66 (18)	C17—C16—H16B	109.4
N8—C5—C6	105.08 (19)	H16A—C16—H16B	108.0
C4—C5—C6	111.2 (2)	C18—C17—C22	118.2 (2)
N8—C5—H5	110.9	C18—C17—C16	122.1 (2)
C4—C5—H5	110.9	C22—C17—C16	119.7 (2)
C6—C5—H5	110.9	C17—C18—C19	120.7 (3)
C5—C6—C7	103.23 (19)	C17—C18—H18	119.7
C5—C6—H6A	111.1	C19—C18—H18	119.7
C7—C6—H6A	111.1	C20—C19—C18	120.3 (3)
C5—C6—H6B	111.1	C20—C19—H19	119.9

C7—C6—H6B	111.1	C18—C19—H19	119.9
H6A—C6—H6B	109.1	C19—C20—C21	119.5 (2)
C1—C7—C6	104.44 (19)	C19—C20—H20	120.3
C1—C7—H7A	110.9	C21—C20—H20	120.3
C6—C7—H7A	110.9	C22—C21—C20	120.0 (3)
C1—C7—H7B	110.9	C22—C21—H21	120.0
C6—C7—H7B	110.9	C20—C21—H21	120.0
H7A—C7—H7B	108.9	C21—C22—C17	121.3 (3)
O9—C9—C10	111.43 (18)	C21—C22—H22	119.3
O9—C9—C2	106.66 (17)	C17—C22—H22	119.3
C10—C9—C2	109.60 (18)	C5—N8—C1	101.36 (17)
O9—C9—H9A	109.7	C5—N8—C16	110.73 (18)
C10—C9—H9A	109.7	C1—N8—C16	111.10 (19)
C2—C9—H9A	109.7	C9—O9—H9O	109.5
C11—C10—C15	118.9 (2)		