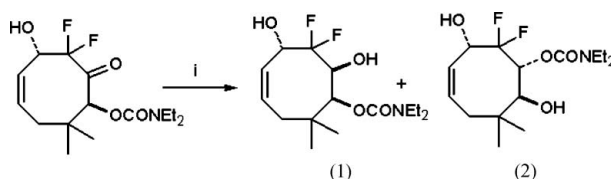


(1*S,2*S**,4*S**)-3,3-Difluoro-2,4-dihydroxy-5,5-dimethylcyclooct-5(*Z*)-en-1-yl *N,N*-diethylcarbamate**John Fawcett,^a Jonathan M Percy,^a Stéphane Pintat,^b Clive A Smith^c and Emi Uneyama^{a*}^aDepartment of Chemistry, University of Leicester, Leicester LE1 7RH, England, ^bGlaxoSmithKline Pharmaceuticals, New Frontiers Science Park, Third Avenue, Harlow CM19 5AW, England, and ^cChroma Therapeutics Ltd, 93 Milton Park, Abingdon, Oxon OX14 4RY, England

Correspondence e-mail: jmp29@leicester.ac.uk

Key indicatorsSingle-crystal X-ray study
T = 150 K
Mean $\sigma(\text{C}-\text{C}) = 0.013 \text{ \AA}$
R factor = 0.082
wR factor = 0.230
Data-to-parameter ratio = 6.9For details of how these key indicators were automatically derived from the article, see <http://journals.iucr.org/e>.The structure of the title compound, C₁₅H₂₅F₂NO₄, is reported and reveals a pseudorotational relationship between the ring conformation of this compound and that of an isomeric by-product reported in the following paper.Received 11 July 2005
Accepted 3 August 2005
Online 21 September 2005**Comment**Conformational equilibria in eight-membered carbocycles occur *via* two main processes, pseudorotation and ring inversion. The latter exchanges substituent groups between equatorial and axial environments in a pseudo-enantiomeric relationship. Ring inversion is usually the more energetically demanding process; barriers to inversion exchange of 7.3–8.5 kcal mol⁻¹ have been reported, with smaller barriers (*ca* 5 kcal mol⁻¹) (Servis & Noe, 1973) for the pseudorotation. [For early attempts to apply variable-temperature NMR to these phenomena, see Anderson *et al.* (1969) and St Jacques *et al.* (1966).] Recent work from our group has attempted to define these processes for a trio of difluorinated cyclooctenyl systems (Fawcett, Griffith *et al.*, 2005). We were interested in observing a pseudorotational relationship between the ring conformations in the pair of reduction products (1) and (2), obtained upon treatment of a precursor ketone with sodium borohydride.Product (1) (the major product) arises from the opposite sense of hydride attack, with the *N,N*-diethylcarbamoyl group retaining its original location (Fig. 1). Product (2), reported in the following paper (Fawcett, Percy *et al.*, 2005), arises from reagent attack on the ring face which bears the hydroxyl group, followed by migration of the *N,N*-diethylcarbamoyl group on to the newly formed hydroxyl group (Balnaves *et al.*, 1999). A comparison of the two molecules is shown in Fig. 2. O—H...O hydrogen bonding links molecules of (1) into chains along the *b* axis (Table 1).**Experimental**The precursor ketone was prepared as described in the literature (Fawcett, Griffith *et al.*, 2005). Sodium borohydride (1.8 mmol, 70 mg) was added in five portions to a cold (273 K) solution of the ketone (1.8 mmol, 0.59 g) in ethanol (10 ml). After completion of the addition, the reaction mixture was allowed to warm to room

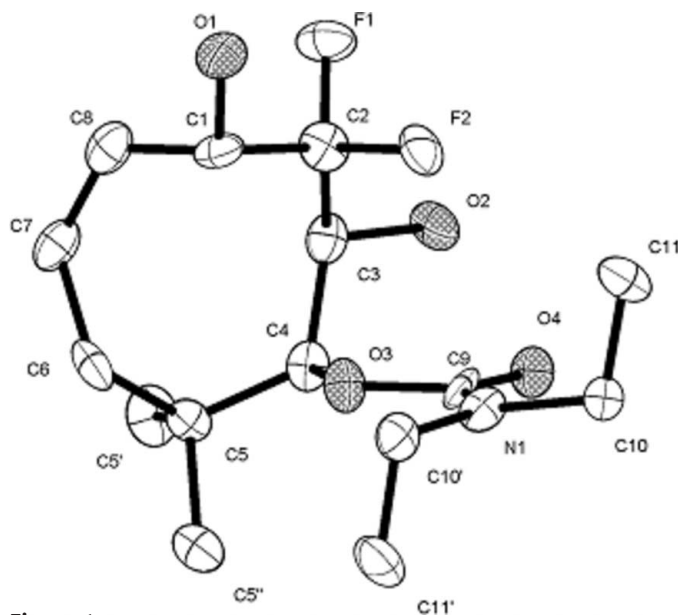


Figure 1
The molecular structure of (1), showing the atom-numbering scheme and 50% displacement ellipsoids. H atoms have been omitted for clarity.

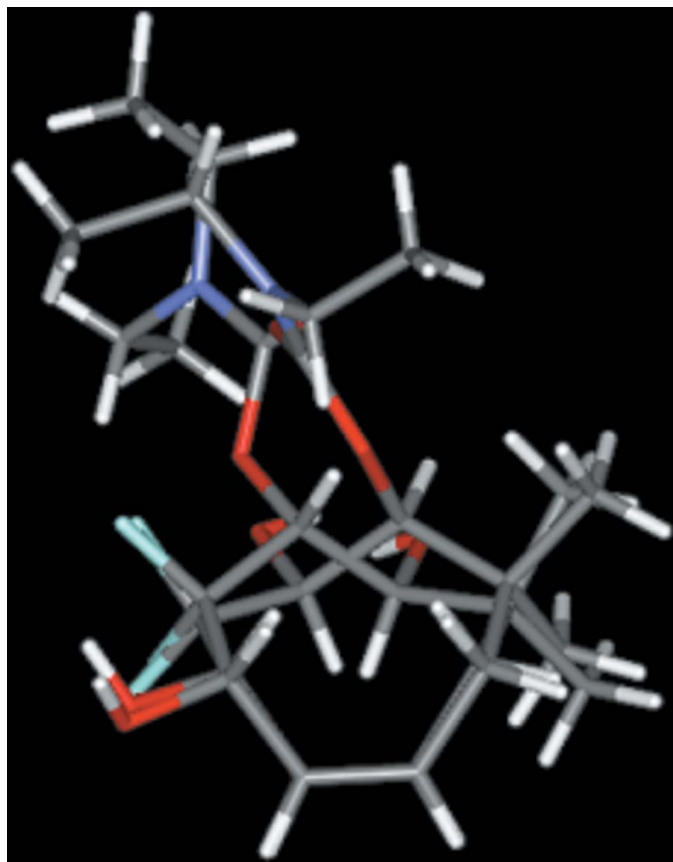


Figure 2
An overlay showing the relationship between the structures of compounds (1) and (2).

temperature, stirred for 2 h at this temperature and poured over a mixture of ice and water (25 ml). HCl (10 ml of a 1 N solution) was added cautiously and the mixture was extracted with diethyl ether (3 × 25 ml). The combined organic extracts were dried (MgSO₄),

filtered and concentrated under reduced pressure to leave a white solid (0.51 g). Purification by column chromatography (40% ethyl acetate in light petroleum) afforded the desired diol (1) as a white solid (0.43 g, 72%). *R_F* (40% ethyl acetate in light petroleum) 0.29; m.p. 388–389 K (found: C 56.17, H 7.71, N 4.29%; C₁₅H₂₅F₂NO₄ requires: C 56.06, H 7.84, N, 4.36%); ν_{\max} (KBr)/cm⁻¹ 3460 (*s br*, O—H), 3356 (*s br*, O—H), 2977 (*m*, =C—H), 2877 (*m*, C—H), 1671 (*s*, C=O); ¹H NMR (250 MHz, CDCl₃): δ 5.83 (1H, *dd*, *J* = 18.5, 9.0 Hz, H-5), 5.53 (1H, *t*, *J* = 9.0, 9.0 Hz, H-4), 4.84 (1H, *ddd*, ³*J*_{HF} = 21.3, 8.0, 4.1 Hz, H-3), 4.48 (1H, *d*, *J* = 5.7 Hz, H-8), 4.18–4.04 (1H, *m*, H-1), 3.42–3.10 [5H, *m*, —OH and —N(CH₂CH₃)₂], 2.45 (1H, *dd*, *J*_{gem} = 13.8, *J* = 8.5 Hz, H-6a), 2.17 (1H, *br s*, —OH), 1.77 (1H, *dd*, *J*_{gem} = 13.8 Hz, *J* = 8.3 Hz, H-6b), 1.18–0.93 [12H, *m*, —N(CH₂CH₃)₂ and 2 × —CH₃]; ¹³C NMR (63 MHz, CDCl₃): δ 157.4, 131.4, 131.3 (*d*, ³*J*_{CF} = 6.6 Hz), 122.8 (*dd*, ¹*J*_{CF} = 253.1, 246.9 Hz), 87.4 (*d*, ³*J*_{CF} = 9.2 Hz), 70.8 (*dd*, ²*J*_{CF} = 23.9, 19.8 Hz), 68.4 (*dd*, ²*J*_{CF} = 23.9, 20.9 Hz), 42.8, 42.0, 39.8, 34.9, 30.4, 24.3, 14.5, 13.4; ¹⁹F NMR (235 MHz, CDCl₃): δ -118.5 (1F, *dddd*, *J*_{gem} = 241.5, ³*J*_{HF} = 21.2, 10.6, ⁴*J*_{FH} = 6.6 Hz), -122.1 (1F, *dd*, *J*_{gem} = 241.5, ³*J*_{FH} = 16.6 Hz); [HRMS (FAB, [M+H]⁺) Found: 322.18293, calculated for C₁₅H₂₆F₂NO₄: 322.18299]; *m/z* (FAB): 322 (100%, [M+H]⁺). An analytical sample was recrystallized by vapour diffusion (ethyl acetate/light petroleum) to afford colourless needles.

Crystal data

C ₁₅ H ₂₅ F ₂ NO ₄	<i>D_x</i> = 1.342 Mg m ⁻³
<i>M_r</i> = 321.36	Mo K α radiation
Monoclinic, <i>Pn</i>	Cell parameters from 2104 reflections
<i>a</i> = 7.9651 (14) Å	θ = 2.6–24.7°
<i>b</i> = 6.4632 (12) Å	μ = 0.11 mm ⁻¹
<i>c</i> = 15.445 (3) Å	<i>T</i> = 150 (2) K
β = 90.136 (3)°	Block cut from needle, colourless
<i>V</i> = 795.1 (2) Å ³	0.24 × 0.18 × 0.12 mm
<i>Z</i> = 2	

Data collection

Bruker APEX CCD area-detector diffractometer	1332 reflections with <i>I</i> > 2 σ (<i>I</i>)
φ and ω scans	<i>R</i> _{int} = 0.041
Absorption correction: none	θ_{\max} = 25.0°
5283 measured reflections	<i>h</i> = -9 → 9
1403 independent reflections	<i>k</i> = -7 → 7
	<i>l</i> = -18 → 18

Refinement

Refinement on <i>F</i> ²	$w = 1/[\sigma^2(F_o^2) + (0.1065P)^2 + 3.2641P]$
$R[F^2 > 2\sigma(F^2)] = 0.082$	where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2) = 0.230$	($\Delta\sigma$) _{max} = 0.003
<i>S</i> = 1.13	$\Delta\rho_{\max} = 0.37 \text{ e \AA}^{-3}$
1403 reflections	$\Delta\rho_{\min} = -0.45 \text{ e \AA}^{-3}$
203 parameters	
H-atom parameters constrained	

Table 1

Hydrogen-bond geometry (Å, °).

<i>D</i> —H... <i>A</i>	<i>D</i> —H	H... <i>A</i>	<i>D</i> ... <i>A</i>	<i>D</i> —H... <i>A</i>
O1—H1...O2 ⁱ	0.84	2.18	2.816 (10)	133

Symmetry code: (i) *x*, *y* + 1, *z*.

H atoms were positioned geometrically, with C—H = 0.95–1.00 Å and O—H = 0.84 Å, and treated as riding, with *U*_{iso}(H) = 1.2 or 1.5 (methyl and OH) times *U*_{eq} of the parent atom.

Data collection: *SMART* (Bruker, 1997); cell refinement: *SAINTE* (Bruker, 1999); data reduction: *SAINTE*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine

structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *SHELXTL* (Sheldrick, 2000); software used to prepare material for publication: *SHELXTL*.

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