Enantioselective synthesis of an octahydroindolizine (indolizidine) alcohol using an enzymatic resolution

*Jing Zhang, Rao Kolluri, Salvador G. Alvarez, Mark Irving, Rajinder Singh and Matthew A. J. Duncton**

Rigel, Inc., 1180 Veterans Boulevard, South San Francisco, CA 94080, United States

E.mail: mattduncton@yahoo.com

Supplemental Information

X-Ray Structure for Compound **9**, as an Acetic Acid Salt Monohydrate

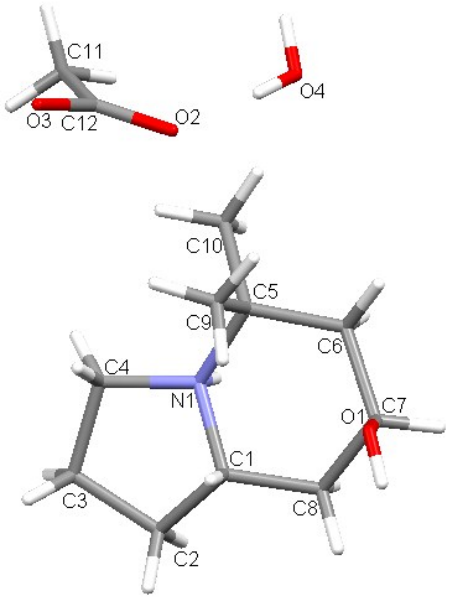

Table 1 Crystal data and structure refinement for compound 9

Identification code	1740-073A (compound **9** in manuscript)
Empirical formula	$C_{12}H_{25}NO_4$
Formula weight	247.33
Temperature/K	100
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	8.20560(10)
b/Å	11.9665(2)
c/Å	13.8857(2)
α/°	90.00
β/°	90.00
γ/°	90.00
Volume/Å^3	1363.47(3)
Z	4
ρ_{calc}mg/mm^3	1.205
m/mm^{-1}	0.729
F(000)	544.0
Crystal size/mm^3	0.408 × 0.22 × 0.128
2Θ range for data collection	9.76 to 140.14°
Index ranges	$-10 \leq h \leq 9$, $-14 \leq k \leq 14$, $-16 \leq l \leq 16$
Reflections collected	11121
Independent reflections	2542[R(int) = 0.0323]
Data/restraints/parameters	2542/0/166
Goodness-of-fit on F^2	1.079
Final R indexes [I>=2σ (I)]	R_1 = 0.0380, wR_2 = 0.1016
Final R indexes [all data]	R_1 = 0.0388, wR_2 = 0.1031
Largest diff. peak/hole / e Å^{-3}	0.27/-0.22
Flack parameter	-0.08(18)

Table 2 Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for compound 9. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
O1	6691.9(15)	1477.7(9)	5134.3(7)	24.9(3)
N1	8547.0(14)	3113.5(10)	6998.1(8)	17.1(3)
C1	9329.5(18)	2116.8(12)	6526.1(10)	18.6(3)
C2	10970.0(19)	2073.5(13)	7045.4(10)	22.3(3)
C3	11430.5(19)	3308.8(14)	7216.3(11)	23.2(3)
C4	9865.4(18)	3977.2(13)	7037.2(10)	19.9(3)
C5	6919.9(18)	3464.7(12)	6566.8(10)	19.6(3)
C6	5829.3(19)	2416.5(13)	6579.0(11)	23.0(3)
C7	6563.8(19)	1352.5(13)	6154.7(10)	21.8(3)
C8	8219.7(19)	1111.9(12)	6612.3(10)	20.7(3)
C9	7141.8(19)	3942.9(13)	5554.6(10)	23.6(3)
C10	6190(2)	4352.3(14)	7232.8(11)	25.5(3)
O2	5431.8(15)	6134.9(9)	4314.3(8)	27.4(3)
O3	6848.1(15)	7621.5(10)	3826.2(7)	26.3(3)
C11	6267(3)	7442.6(18)	5501.4(11)	42.9(5)
C12	6163(2)	7022.0(14)	4473.5(10)	23.2(3)
O4	3188.7(15)	5363.5(9)	5633.8(8)	24.3(3)

Table 3 Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for compound 9. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+...+2hka \times b \times U_{12}]$

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O1	30.9(6)	23.7(5)	20.2(5)	-4.8(4)	-6.8(4)	4.8(5)
N1	17.7(6)	18.3(6)	15.2(5)	0.3(4)	-1.0(4)	1.7(5)
C1	19.3(7)	20.6(7)	16.1(6)	-0.2(5)	0.1(5)	4.6(6)
C2	19.8(7)	25.9(7)	21.3(7)	-0.3(6)	-1.7(5)	5.7(6)
C3	19.3(7)	28.5(8)	21.9(7)	2.2(6)	-1.9(5)	0.2(6)
C4	20.3(7)	20.6(7)	18.8(7)	1.9(5)	-1.1(5)	-2.4(6)
C5	16.8(7)	21.6(7)	20.5(7)	-1.9(6)	-2.7(6)	3.2(6)
C6	18.7(7)	27.5(8)	22.8(7)	-2.3(6)	-0.5(6)	-0.4(6)
C7	24.6(8)	20.1(7)	20.7(7)	-1.0(5)	-2.4(6)	-2.8(6)
C8	26.4(8)	18.2(6)	17.5(6)	0.1(5)	-1.7(6)	3.2(6)
C9	25.6(8)	23.9(7)	21.3(7)	1.0(6)	-5.7(6)	4.1(6)
C10	23.1(8)	25.9(8)	27.6(8)	-6.1(6)	-3.0(6)	6.2(7)
O2	33.9(6)	25.8(5)	22.4(5)	-0.6(4)	-0.3(4)	-6.1(5)
O3	32.7(6)	28.5(6)	17.8(5)	-1.5(4)	0.1(4)	-8.3(5)
C11	56.9(13)	50.3(11)	21.3(8)	-4.6(8)	4.0(8)	-29.4(10)
C12	24.4(7)	27.1(8)	18.0(7)	0.7(6)	-2.3(6)	-1.9(6)
O4	27.8(6)	20.4(5)	24.9(5)	-1.4(4)	3.2(5)	0.6(5)

Table 4 Bond Lengths for compound 9.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O1	C7	1.4287(18)	C5	C6	1.541(2)
N1	C1	1.5047(18)	C5	C9	1.5284(19)
N1	C4	1.4973(19)	C5	C10	1.530(2)
N1	C5	1.5224(17)	C6	C7	1.527(2)
C1	C2	1.5279(19)	C7	C8	1.527(2)
C1	C8	1.513(2)	O2	C12	1.239(2)
C2	C3	1.544(2)	O3	C12	1.2800(19)
C3	C4	1.533(2)	C11	C12	1.5158(19)

Table 5 Bond Angles for compound 9.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C1	N1	C5	114.94(11)	C9	C5	C6	112.58(12)
C4	N1	C1	104.75(11)	C9	C5	C10	110.02(13)
C4	N1	C5	117.22(11)	C10	C5	C6	109.33(13)
N1	C1	C2	101.38(11)	C7	C6	C5	116.44(13)
N1	C1	C8	109.79(11)	O1	C7	C6	108.92(12)
C8	C1	C2	117.77(12)	O1	C7	C8	111.52(13)
C1	C2	C3	104.81(12)	C6	C7	C8	110.35(12)
C4	C3	C2	105.63(12)	C1	C8	C7	110.65(12)
N1	C4	C3	104.53(11)	O2	C12	O3	124.57(14)
N1	C5	C6	106.28(11)	O2	C12	C11	118.65(14)
N1	C5	C9	111.14(12)	O3	C12	C11	116.78(15)
N1	C5	C10	107.29(11)				

Table 6 Hydrogen Bonds for compound 9.

D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A/°
O1	H1	O4[1]	0.84	1.90	2.7387(16)	179.1
N1	H1A	O3[2]	0.93	1.78	2.7060(15)	172.1
O4	H4C	O3[3]	0.83(3)	1.93(3)	2.7544(17)	169(3)
O4	H4D	O2	0.85(3)	1.90(3)	2.7563(16)	177(2)

[1]1/2+X,1/2-Y,1-Z; [2]3/2-X,1-Y,1/2+Z; [3]-1/2+X,3/2-Y,1-Z

Table 7 Torsion Angles for compound 9.

A	B	C	D	Angle/°
O1	C7	C8	C1	67.33(15)
N1	C1	C2	C3	-35.48(14)
N1	C1	C8	C7	57.95(14)
N1	C5	C6	C7	-50.27(15)
C1	N1	C4	C3	-35.28(13)
C1	N1	C5	C6	54.07(14)
C1	N1	C5	C9	-68.74(15)
C1	N1	C5	C10	170.94(12)
C1	C2	C3	C4	14.57(15)
C2	C1	C8	C7	173.19(12)
C2	C3	C4	N1	12.26(15)
C4	N1	C1	C2	44.12(13)
C4	N1	C1	C8	169.40(11)
C4	N1	C5	C6	177.78(11)
C4	N1	C5	C9	54.97(15)
C4	N1	C5	C10	-65.35(16)
C5	N1	C1	C2	174.22(11)
C5	N1	C1	C8	-60.50(15)
C5	N1	C4	C3	-164.02(11)
C5	C6	C7	O1	-70.45(16)
C5	C6	C7	C8	52.28(17)
C6	C7	C8	C1	-53.87(15)
C8	C1	C2	C3	-155.24(12)
C9	C5	C6	C7	71.63(17)
C10	C5	C6	C7	-165.77(13)

Table 8 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for compound 9.

Atom	*x*	*y*	*z*	U(eq)
H1	7161	916	4900	37
H1A	8336	2908	7632	20
H1B	9517	2284	5829	22
H2A	11800	1696	6643	27
H2B	10872	1669	7664	27
H3A	11820	3420	7884	28
H3B	12300	3545	6766	28
H4A	9667	4514	7567	24
H4B	9932	4393	6422	24
H6A	5518	2262	7255	28
H6B	4816	2589	6221	28
H7	5816	713	6296	26
H8A	8069	922	7300	25
H8B	8728	463	6289	25
H9A	7739	4651	5593	35
H9B	6071	4073	5263	35
H9C	7757	3412	5160	35
H10A	6109	4052	7888	38
H10B	5102	4558	7002	38
H10C	6892	5015	7235	38
H11A	5698	8160	5553	64
H11B	7413	7541	5681	64
H11C	5756	6899	5934	64
H4C	2660(30)	5930(20)	5804(18)	52(7)
H4D	3880(30)	5584(19)	5215(16)	43(6)

Experimental

Single crystals of $C_{12}H_{25}NO_4$ [compound **9**] were supplied by M. Duncton of Rigel Pharmaceuticals. A suitable crystal was selected and mounted using a MiteGen mylar tip with paratone oil on a 'Bruker APEX-II CCD' diffractometer. The crystal was kept at 100 K during data collection using Olex2.[1] The structure was solved with the olex2.solve structure solution program using Charge Flipping and refined with the XL[2] refinement package using Least Squares minimization.

1. O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard, J. Puschmann, *J. Appl. Cryst.*, 2009, **42**, 339-341.
2. G. M. Sheldrick, *Acta Cryst.*, 2008, **A64**, 112-122.

Crystal structure determination of **compound 9.**

Crystal Data. $C_{12}H_{25}NO_4$, M =247.33, orthorhombic, a = 8.20560(10) Å, b = 11.9665(2) Å, c = 13.8857(2) Å, V = 1363.47(3) Å^3, T = 100, space group $P2_12_12_1$ (no. 19), Z = 4, μ(CuKα) = 0.729, 11121 reflections measured, 2542 unique (R_{int} = 0.0323) which were used in all calculations. The final wR_2 was 0.1031 (all data) and R_1 was 0.0380 (>2sigma(I)).

This report has been created with Olex2, compiled on May 9 2012 12:37:22.