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Synthesis and Crystal Structure Characterization of (1R,2R,3R,5S)-3-(3-chlorophenyl)-1-hydroxy-2-methyl-6-phenyl-8-oxa-6-azabicyclo [3.2.1]octan-7-one

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The title compound, (1R,2R,3R,5S)-3-(3-chlorophenyl)-1-hydroxy-2-methyl-6-phenyl-8-oxa-6-azabicyclo[3.2.1]octan-7-one, was synthesized and characterized by ^{1}H and ^{13}C NMR and HRMS spectroscopy. Its absolute molecular configuration was investigated by X-ray crystallography. The crystal structure analysis revealed that the structure exhibits intermolecular hydrogen bonds of the type O—H... O. The methyl group and chlorophenyl group are located in the cis configuration. The conformation is stabilized by weak intermolecular C—H. .. O interactions.

Keywords Bicyclic lactam; chirality; single crystal; X-ray diffraction

Introduction

Bicyclic lactams have been used to synthesize iminosugars [1] and they are found to be structural moiety of many natural products [2]. Therefore, synthetic routes to such kind of compounds are of interest. In this paper, we describe a simple, excellently enantioselective and diastereoselective one-pot synthesis of new bicyclic lactam at 0°C in the presence of TBS-protected diarylprolinol as an organocatalyst and triethylamine (TEA) as an additive. Furthermore, the bicyclic lactam, (1R,2R,3R,5S)-3-(3-chlorophenyl)-1-hydroxy-2-methyl-6-phenyl-8-oxa-6-azabicyclo[3.2.1]octan-7-one (Fig. 1), was characterized by ^{1}H and ^{13}C NMR, and HRMS spectroscopy. Its crystal structure was investigated by X-ray single-crystal diffraction analysis.

Experimental

^{1}H and ^{13}C NMR were recorded in $CDCl_3$ on Bruker AVANCE III (500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR). Proton chemical shifts (δ) are relative to tetramethylsilane

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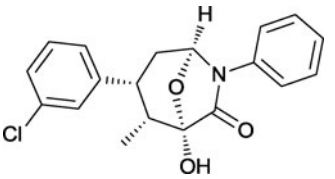


Figure 1. Structure of bicyclic lactam.

(TMS, $\delta = 0.0$) as internal standard and expressed in parts per million. Spin multiplicities are given as *s* (singlet), *d* (doublet), *t* (triplet), and *q* (quartet) as well as *b* (broad). Coupling constants (*J*) are given in hertz. HRMS data were measured on an Agilent 6120 LC/TOF-MS with ESI source.

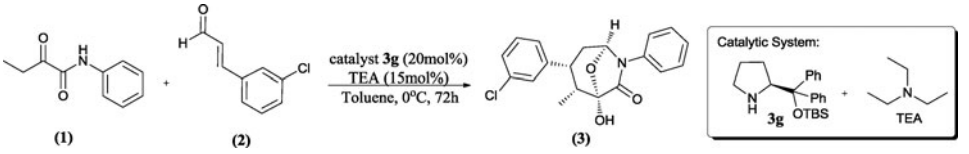
Synthesis of 2-oxo-N-phenylbutanamide (1) [3]

To a stirred solution of 2-oxobutanoic acid (0.34 g, 3 mmol) and aniline (0.56 g, 6 mmol) in methylene chloride (20 mL) at 0°C was added a solution of dicyclohexylcarbodiimide (0.6 g, 3 mmol) in methylene chloride (7 mL) dropwise over 30 min. Stirring was continued at ambient temperature for 16 h. The white solid precipitates were filtered off and the solution was washed with a 1 N HC1 solution and then with water and dried. The solvent was removed under reduced pressure. This was isolated by flesh chromatographed column using petroleum ether-ethyl acetate (20:1) as eluent to obtain 2-oxo-N-phenylbutanamide (0.3 g, 56%).

Synthesis of (1R,2R,3R,5S)-3-(3-chlorophenyl)-1-hydroxy-2-methyl-6-phenyl-8-oxa-6-azabicyclo[3.2.1]octan-7-one (3)

To the solution of the chiral amine catalyst **3 g** (20 mol%) and triethylamine (15 mol%) in toluene (0.5 ml) was added sequentially α-ketoamide (**1**) (0.2 mmol) and (*E*)-3-(3-chlorophenyl)acrylaldehyde (2) (0.24 mmol) at 0°C with vigorous stirring. The reaction was monitored by TLC. After completion, the reaction mixture was extracted with EtOAc (3×10 mL), washed with water, dried and concentrated. The residue was purified by flash chromatography to give the product. The enantiomeric ratio was determined by HPLC analysis on a chiral column. Single crystals were obtained by slow evaporation of a methanol and petroleum ether (V/V = 1:2) solution.

95% yield, >99% *ee*. The enantiomeric excess was determined by HPLC on Daicel Chiralpak OD-H with hexane/i-PrOH (80:20) as the eluent. Flow: 1.0 ml/min; UV = 232 nm; $t_{minor} = 17.252$ min, $t_{major} = 10.773$ min; **^{1}H NMR** (500 MHz, $CDCl_3$): $\delta =$ 7.546–7.544 (m, 2H), 7.369–7.336 (m, 2H), 7.250–7.143 (m, 4H), 7.045–7.030 (m, 1H), 5.920 (s, 1H), 4.997 (s, 1H), 3.252–3.206 (m, 1H), 2.413–2.357 (m, 2H), 2.024–1.984



Scheme 1. Synthesis of bicyclic lactam (3).

(m, 1H), 0.887–0.873 (d, $J = 7.0$Hz, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$): $\delta = 170.464$, 142.068, 135.664, 134.484, 129.751, 129.437(×2), 127.742, 126.986, 125.837, 125.440, 118.600(×2), 101.903, 85.459, 37.901(×2), 25.709, and 6.776 ppm; **HRMS:** (ESI+) m/z calcd for $[C_{19}H_{19}ClNO_3]^+$ 344.1053, found 344.1065.

Crystal Structure Analysis

The crystal structure of the title compound was solved by direct methods and was refined by a full matrix least-squares method on F^2. A summary of the salient crystallographic data is given in Table 1.

Table 1. Crystal data and structure refinement parameters of compound (3)

Parameter	Value
CCDC deposition number	CCDC 988911
Empirical formula	$C_{19}H_{18}ClNO_3$
Formula weight	343.79
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)
Cell dimensions	$a = 10.572(3)$ Å
	$b = 6.8163(19)$ Å
	$c = 11.398(3)$ Å
	$\beta = 97.963(6)^\circ$
Volume	813.5(4) Å^3
Z	2
Density (calculated)	1.404 Mg/m^3
Absorption coefficient	0.252 mm^{-1}
F_{000}	360
Crystal size	0.231 × 0.176 × 0.123 mm
Theta range for data collection	1.80°–26.00°
Index ranges	$-12 \le h \le 13$
	$-8 \le k \le 8$
	$-14 \le l \le 13$
Reflections collected	4817
Independent reflections	2894 [$R_{int} = 0.0342$]
Absorption correction	$T_{min} = 0.62665$, $T_{max} = 1.00000$
Refinement method	Full-matrix least-squares on F^2
Data/restraints /parameters	2894/1/220
Goodness of fit on F^2	1.068
Final R indices [$I > 2\sigma\ (I)$]	$R_1 = 0.0501$, $\omega R_2 = 0.1304$
R indices (all data)	$R_1 = 0.0474$, $\omega R_2 = 0.1270$
Extinction correction	None
Flack parameter	0.08(9)
Largest diff. peak and hole	0.393 and −0.334 e.Å $^{-3}$

A single crystal suitable for X-ray diffraction obtained in methanol and petroleum ether (V/V = 1:2) was colorless and block. The single crystal XRD of the crystal was collected on a PROCESS-AUTO [4] diffractometer at 293(2) K using graphite-monochromated Mo *Kα* radiation (λ = 0.71073 Å). The cell was refined on a PROCESS-AUTO [4] and the data were reducted on a CrystalStructure [5] and corrected for absorption using multi-scan [6]. The structure was solved by direct methods using SHELXS-97 and refined by a full-matrix least-squares procedure using the program SHELXL-97 [7]. Subsequent refinements were carried out with anisotropic thermal parameters for nonhydrogen atoms. H atoms were placed in calculated positions with C—H = 0.96 Å (sp^3), C—H = 0.93 Å (aromatic). All H atoms included in the final cycles of refinement using a riding model, with *U*iso(H) = 1.5 *U*eq(sp^3) or 1.2 *U*eq of the carrier atoms. A molecular plot was prepared with ORTEP-3 for Windows [8]. The software used to prepare material for publication was WINGX [9]. Table 2 gives the atomic coordinates and equivalent thermal parameters of the nonhydrogen atoms. Tables 3 and 4 give the list of bond lengths and bond angles, respectively.

Table 2. Atomic coordinates and equivalent thermal parameters of the nonhydrogen atoms (Å^2). $U_{eq} = (1/3) \sum i \sum j\ Uij a_i^* a_j^* (a_i . a_j)$

Atom	*x*	*y*	*z*	U_{eq}
Cl1	0.67919(8)	0.39772(16)	0.90227(7)	0.0773(3)
N1	0.17386(17)	0.7581(3)	0.38083(18)	0.0399(5)
O1	0.00657(13)	0.9215(3)	0.45033(17)	0.0495(5)
O2	0.32959(14)	0.9736(3)	0.44636(15)	0.0397(4)
O3	0.21071(16)	1.2024(3)	0.52319(19)	0.0505(5)
C1	0.11940(19)	0.8920(4)	0.4455(2)	0.0381(5)
C2	0.2300(2)	1.0032(4)	0.5172(2)	0.0377(5)
C3	0.31419(19)	0.7735(4)	0.4134(2)	0.0380(5)
C4	0.3655(2)	0.6468(4)	0.5185(2)	0.0372(5)
C5	0.2903(2)	0.6846(3)	0.6215(2)	0.0353(5)
C6	0.2700(2)	0.9089(4)	0.6381(2)	0.0378(5)
C7	0.3857(3)	1.0140(4)	0.7041(3)	0.0540(7)
C8	0.1137(2)	0.6283(4)	0.2945(2)	0.0418(5)
C9	−0.0005(3)	0.6807(6)	0.2291(3)	0.0575(7)
C10	−0.0568(3)	0.5556(7)	0.1412(3)	0.0694(10)
C11	−0.0012(3)	0.3818(7)	0.1184(3)	0.0710(10)
C12	0.1129(4)	0.3324(6)	0.1841(3)	0.0745(10)
C13	0.1698(3)	0.4520(5)	0.2721(3)	0.0591(8)
C14	0.3462(2)	0.5880(4)	0.7353(2)	0.0388(5)
C15	0.4736(2)	0.5433(4)	0.7632(2)	0.0406(5)
C16	0.5175(3)	0.4538(4)	0.8701(2)	0.0513(6)
C17	0.4363(3)	0.4104(5)	0.9516(2)	0.0634(8)
C18	0.3108(3)	0.4576(5)	0.9247(3)	0.0663(8)
C19	0.2654(3)	0.5443(5)	0.8184(3)	0.0549(7)

Table 3. Bond lengths (Å)

Atoms	Length	Atoms	Length
Cl1-C16	1.741(3)	C6-C7	1.523(3)
N1-C1	1.352(3)	C8-C9	1.376(4)
N1-C8	1.407(3)	C8-C13	1.379(4)
N1-C3	1.482(3)	C9-C10	1.385(5)
O1-C1	1.218(3)	C10-C11	1.364(6)
O2-C3	1.418(3)	C11-C12	1.370(5)
O2-C2	1.427(3)	C12-C13	1.366(5)
O3-C2	1.376(3)	C14-C15	1.375(3)
C1-C2	1.531(3)	C14-C19	1.393(4)
C2-C6	1.526(3)	C15-C16	1.384(4)
C3-C4	1.515(3)	C16-C17	1.382(4)
C4-C5	1.529(3)	C17-C18	1.359(5)
C5-C14	1.501(3)	C18-C19	1.373(4)
C5-C6	1.559(3)		

Table 4. Bond angles (°)

Atoms	Angle	Atoms	Angle
C1-N1-O8	128.36(19)	C7-C6-C5	114.0(2)
C1-N1-C3	107.63(19)	C2-C6-C5	109.21(19)
C8-N1-C3	124.0(2)	C9-C8-C13	119.5(3)
C3-O2-C2	102.66(16)	C9-C8-N1	119.6(3)
O1-C1-N1	129.0(2)	C13-C8-N1	120.8(2)
O1-C1-C2	125.1(2)	C8-C9-C10	119.3(3)
N1-C1-C2	105.89(18)	C11-C10-C9	121.3(3)
O3-C2-O2	107.08(19)	C10-C11-C12	118.6(3)
O3- C2-C6	113.3(2)	C13-C12-C11	121.3(3)
O2-C2-C6	108.53(17)	C12-C13-C8	119.9(3)
O3-C2-C1	114.0(2)	C15-C14-C19	118.0(2)
O2-C2-C1	101.36(19)	C15-C14-C5	123.5(2)
C6-C2-C1	111.64(19)	C19-C14-C5	118.5(2)
O2-C3-N1	102.04(18)	C14-C15-C16	119.9(2)
O2-C3-C4	108.88(19)	C17-C16-C15	121.5(3)
N1-C3-C4	113.20(19)	C17-C16-C11	119.6(2)
C3-C4-C5	110.11(18)	C15-C16-C11	118.8(2)
C14-C5-C4	113.93(18)	C18-C17-C16	118.4(3)
C14-C5-C6	111.72(19)	C17-C18-C19	120.8(3)
C4-C5-C6	110.72(18)	C18-C19-C14	121.4(3)
C7-C6-C2	110.5(2)		

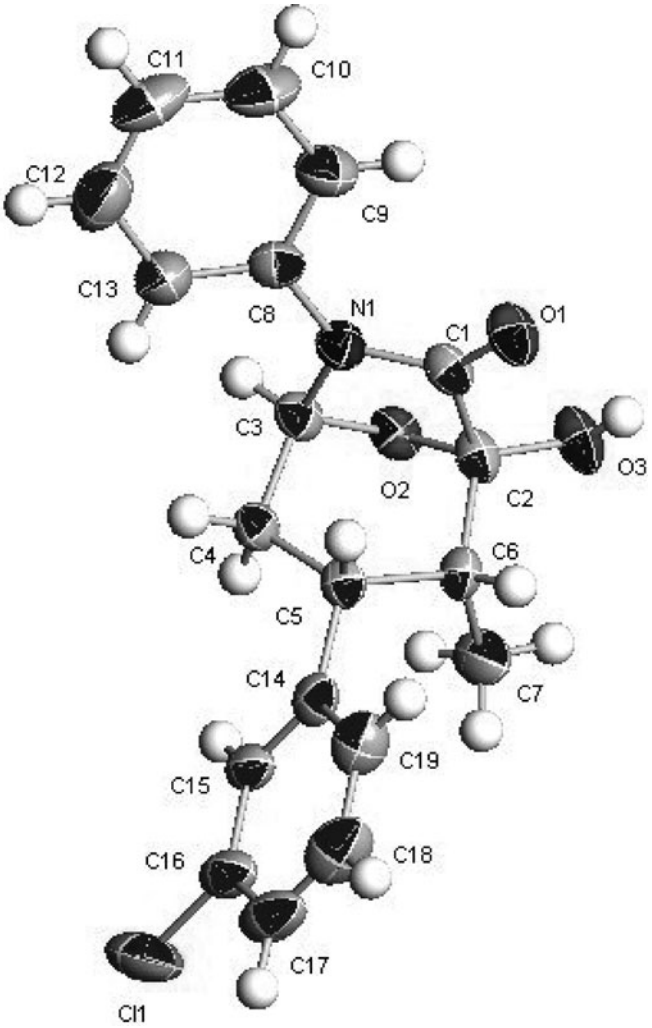


Figure 2. ORTEP of the molecule with thermal ellipsoids drawn at 50% probability.

The ORTEP of the molecule with thermal ellipsoids drawn at 50% probability is shown in Fig. 2. The crystal structure analysis revealed that the structure exhibits intermolecular hydrogen bonds of the type O3–H3 . . . O1. The molecules are linked by weak intermolecular C—H . . . O interactions. The methyl group and chloro phenyl group are located in the *cis* configuration. Furthermore, the torsion angle of C7–C6–C5–C14 is 48.3(8)°. The six-membered ring including an oxygen atom adopts a perfect chair conformation. C2, C3, C4, and C6 are on the same plane. The angle is 71.0(3)° between the plane of the C2–C3–C4–C6 and the O1–C1–N1 plane. The torsion angle of C3–N1–C1–C2 is 2.8(3)°. The N1–C3–C4 and C1–C2–C6 bond angles are 113.2(0)° and 111.6(5)°, respectively. The Packing diagram of (3) is given in Fig. 3.

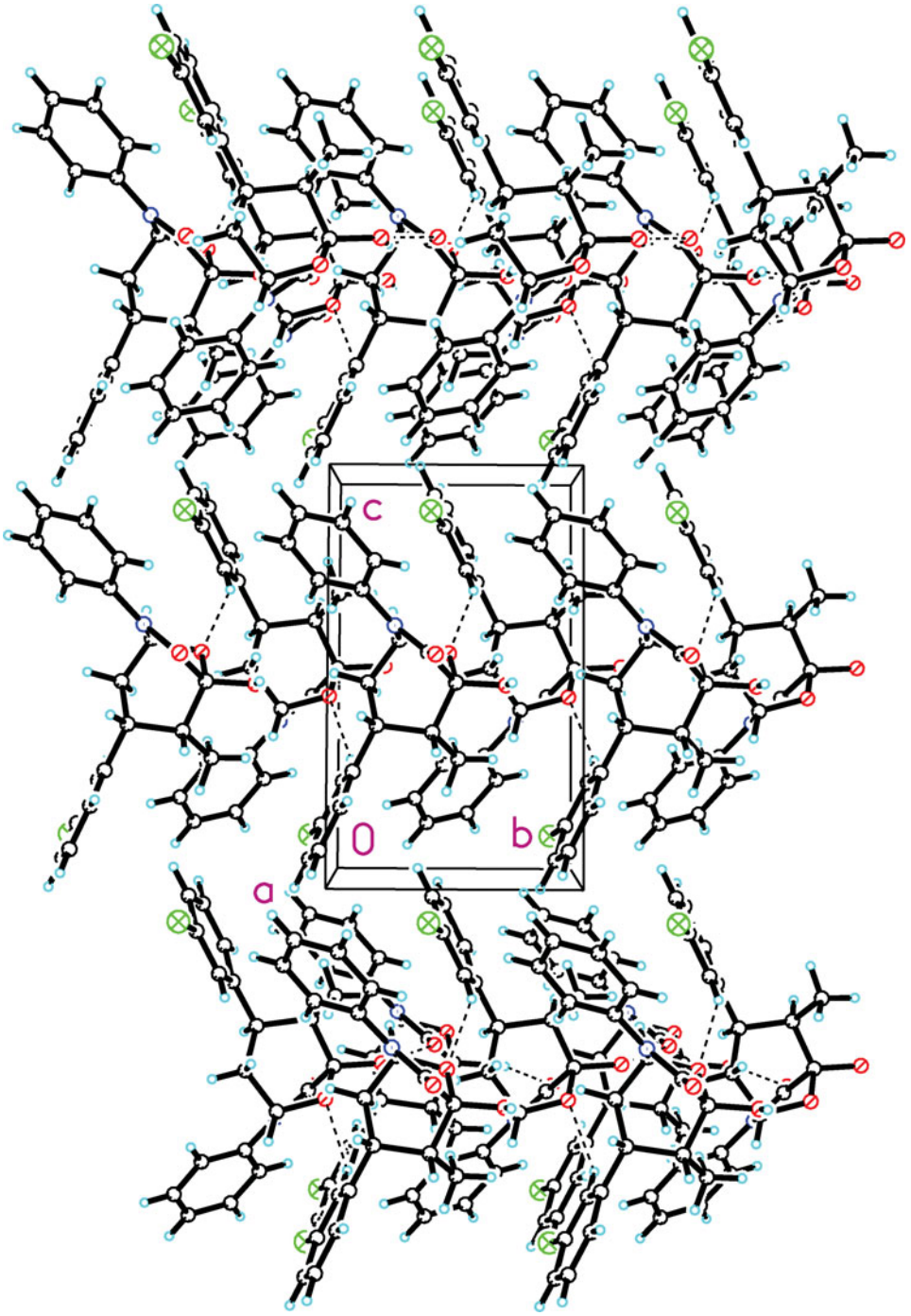


Figure 3. The crystal packing of the title compound (3).

Conclusion

The title compound (1R,2R,3R,5S)-3-(3-chlorophenyl)-1-hydroxy-2-methyl-6-phenyl-8-oxa-6-azabicyclo[3.2.1]octan-7-one (3), was synthesized and characterized by ^{1}H and ^{13}C NMR and HRMS spectroscopy. We summarized the results from X-ray diffraction measurements for compound (3) single crystal. X-ray analysis revealed that the methyl group and chlorophenyl group are located in the *cis* configuration, and the molecules are linked by weak intermolecular C—H . . . O interactions.

Supplementary Information

CCDC 988911 contains the supplementary crystallographic data for this article. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html, or from The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK. Fax:+44(0)1223-336033. E-mail: deposit@ccdc.cam.ac.uk.

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