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Research Article

Synthesis and Molecular Structure of Chiral (2*S*, 5*S*)-*tert*-Butyl 3-Oxo-2-oxa-5-azabicyclo[2.2.2]octane-5-carboxylate

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The title compound (2*S*, 5*S*)-*tert*-butyl 3-oxo-2-oxa-5-azabicyclo[2.2.2]octane-5-carboxylate was synthesized as a chiral cyclic amino acid ester from the corresponding *cis*- and *trans*-5-hydroxypipecolic acid ethyl esters via an intramolecular lactonization reaction without using chiral catalyst or enzyme and without separation by chiral column chromatography. The chiral compound was characterized using ^{1}H NMR spectroscopy and high-resolution mass spectrometry. Its exact structure was then determined via single crystal X-ray diffraction analysis of a single crystal obtained after recrystallization of the compound from ethyl acetate/diethyl ether. The crystal was found to be of the orthorhombic space group $P2_12_12_1$ (No. 19, noncentrosymmetric, chiral) with a = 9.6402(10) Å, b = 9.7026(10) Å, c = 12.2155(12) Å, D_{calc} = 1.3194 g/cm^3, and a Flack parameter of 0.0(5) at 90 K. The compound has a bicyclo[2.2.2]octane structure comprised of lactone and piperidine groups.

1. Introduction

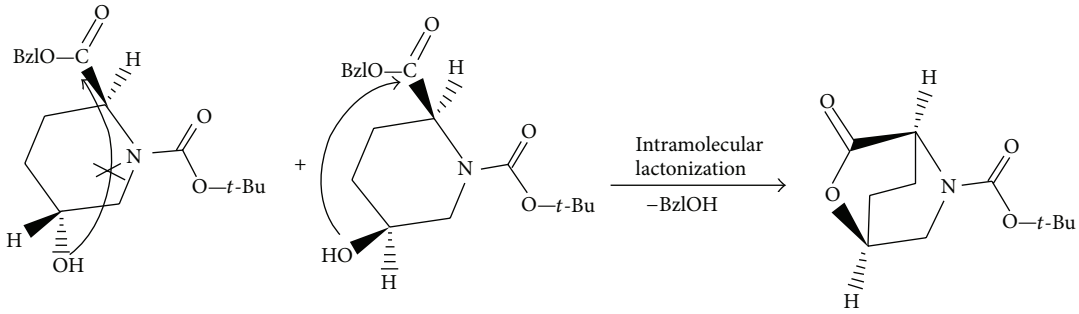
Hydroxypipecolic acid (5-hydroxy-2-piperidinecarboxylic acid) is a six-membered homologue of 4-hydroxyproline found in some natural plants, such as date and acacia trees, whereas 4-hydroxyproline is found in animals (collagen) [1, 2]. Several hydroxypipecolic acid derivatives have been synthesized via intramolecular reactions of precursors functionalized with epoxide groups [3–5]. However, a diastereomeric mixture of *cis*- and *trans*-5-hydroxymethylpipecolic acids has generally been obtained, and in some cases, the formation of undesired 5-hydroxymethylprolines has also been noted [4–6]. Because the intramolecular reaction of epoxide precursors suffers from the formation of stereo- and regioisomers, a straightforward method for the preparation, isolation, and characterization of the pure single enantiomers of hydroxypipecolic acid and derivatives of this rare amino acid is required.

Previously, we synthesized a 4-hydroxyproline derivative from an amino acid bearing an epoxide [7]. During this study, we observed that the *cis* isomer underwent intramolecular lactonization. In addition, we reported the crystal structure of "racemic" *tert*-butyl 3-oxo-2-oxa-5-azabicyclo[2.2.1]heptane-5-carboxylate prepared using an alternative synthetic pathway [8].

Based on these previous results, it was expected that *cis*-5-hydroxypipecolic acids would also undergo intramolecular lactonization, while the corresponding *trans* isomers would not. Indeed, when a mixture of a *cis*- and *trans*-5-hydroxypipecolic acid derivative was reacted under acidic conditions, the *cis* isomer was successfully converted to the lactone (2*S*, 5*S*)-*tert*-butyl 3-oxo-2-oxa-5-azabicyclo[2.2.2]octane-5-carboxylate, which was readily separated from the remaining *trans* isomer by washing the organic layer with an alkaline solution. A crystal structure analysis was performed to determine the exact chiral structure of the molecule, and the results were compared to those for a crystal of the "racemic" compound reported previously [8].

2. Materials and Methods

All reagents and solvents were obtained from commercial sources and used as received. The ^{1}H-NMR spectrum was



Scheme 1

recorded on a JEOL JNM α-500 spectrometer in $CDCl_3$ with tetramethylsilane (Me_4Si) as the internal reference. The positive fast atom bombardment (FAB) mass spectrum (MS) and high-resolution FAB mass spectrum of the compound were obtained on a JEOL JMS-SX102A spectrometer using nitrobenzyl alcohol (NBA) as the matrix and dichloromethane (DCM) as the solvent. The instrument was operated in positive ion mode over an m/z range of 50–1000.

2.1. (2S, 5S)-tert-Butyl 3-Oxo-2-oxa-5-azabicyclo[2.2.2]octane-5-carboxylate (Scheme 1). A diastereomeric mixture of *tert*-butoxycarbonyl-*l*-5-hydroxypipecolic acid benzyl ester (0.83 g, 2.50 mmol) was dissolved in 15 mL of acetic acid, and then Pd/C (10% w/w, 0.25 g) was added to the solution. The resulting black suspension was stirred for 6 h under a hydrogen gas stream. The suspension was then filtered, and the filtrate was concentrated via rotary evaporation to a colorless oil. Next, a solution of 4% $NaHCO_3$ (aq) was added to the resulting residue, and the mixture was extracted with diethyl ether (20 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and evaporated under vacuum to give (2*S*, 5*S*)-*tert*-butyl 3-oxo-2-oxa-5-azabicyclo[2.2.2]octane-5-carboxylate (120 mg, 21%) as a white solid.

Single crystals of (2*S*, 5*S*)-*tert*-butyl 3-oxo-2-oxa-5-azabicyclo[2.2.2]octane-5-carboxylate were obtained from a solution of ethyl acetate/hexane at room temperature using a vapor diffusion technique. In principle, amino acids are moderately acid-sensitive, and *tert*-butoxycarbonyl (Boc) group removal occurs in the presence of acidic air. Therefore, we carefully recrystallized the lactone from the solution in the absence of acidic air.

^{1}H NMR (500 MHz, $CDCl_3$) 1.47 (s, 9H, *tert*-butyl H), 1.80 (m, 1H, azabicyclo C–H), 2.00 (m, 1H, azabicyclo C–H), 2.11 (m, 1H, azabicyclo C–H), 2.22 (br s, 1H, azabicyclo C–H), 3.45 (m, 1H, azabicyclo C–H), 3.63 (m, 1H, azabicyclo C–H), 4.61–4.82 (m, 2H, azabicyclo C–H). pos. FAB-MS: m/z 228 ($[M + H]^+$). HR-FAB-MS $[C_{11}H_{18}N_1O_4]^+$ ($[M + H]^+$): calculated = 228.12358, found = 228.1253.

Single crystals of (2*S*, 5*S*)-*tert*-butyl 3-oxo-2-oxa-5-azabicyclo[2.2.2]octane-5-carboxylate were obtained from a solution of ethyl acetate/diethyl ether at room temperature using a slow diffusion method. In principle, amino acids are moderately acid-sensitive and Boc group removal occurs in the presence of acidic air. Therefore, we carefully recrystallized the lactone from the solution in the absence of acidic air.

2.2. X-Ray Crystallography: Single-Crystal X-Ray Analysis and Structure Determination (Table 1). A colorless prismatic crystal of (2*S*, 5*S*)-*tert*-butyl 3-oxo-2-oxa-5-azabicyclo[2.2.2]-heptane-5-carboxylate with the approximate dimensions 0.30 × 0.30 × 0.20 mm was mounted on a glass fiber. The data collection was performed on a Bruker APEX II KY CCD diffractometer using graphite monochromatized Mo-Kα-radiation (λ = 0.71073 Å) and a nominal crystal-to-area detector distance of 58 mm.

The data were collected at a temperature of 90 K to a maximum 2θ value of 25.00° (0.84 Å resolution). APEX2 software was used for preliminary determination of the unit cell [9]. Determination of the integrated intensities and unit cell refinement were performed using the SAINT program [10]. Of the 11171 reflections that were collected, 2035 were unique (R_{int} = 0.0216); equivalent reflections were merged. The linear absorption coefficient, μ, for Mo-Kα radiation was 0.100 cm^{-1}.

An empirical absorption correction was applied that resulted in transmission factors ranging from 0.555 to 0.980. The data were corrected for Lorentz and polarization effects.

The structure was solved using the SHELXS direct method [11], and subsequent structure refinements were performed using SHELXL [12]. All nonhydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms at carbon atoms were added geometrically and refined using a riding model (constrained).

The final cycle of full-matrix least-squares refinement on F^2 was based on 2035 observed reflections and 149 variable parameters and converged with unweighted and weighted agreement factors of $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o| = 0.0242$ and $wR_2 = [\Sigma(w(F_o^2 - F_c^2)^2)/\Sigma w(F_o^2)^2]^{1/2} = 0.0601$, respectively.

All nonhydrogen atoms were refined with anisotropic displacement parameters. The standard deviation for the observations of the unit weights was 1.038 (standard deviation of an observation of unit weight: $[\Sigma w(F_o^2 - F_c^2)^2/N_o - N_v]^{1/2}$ where N_o = number of observations; N_v = number of

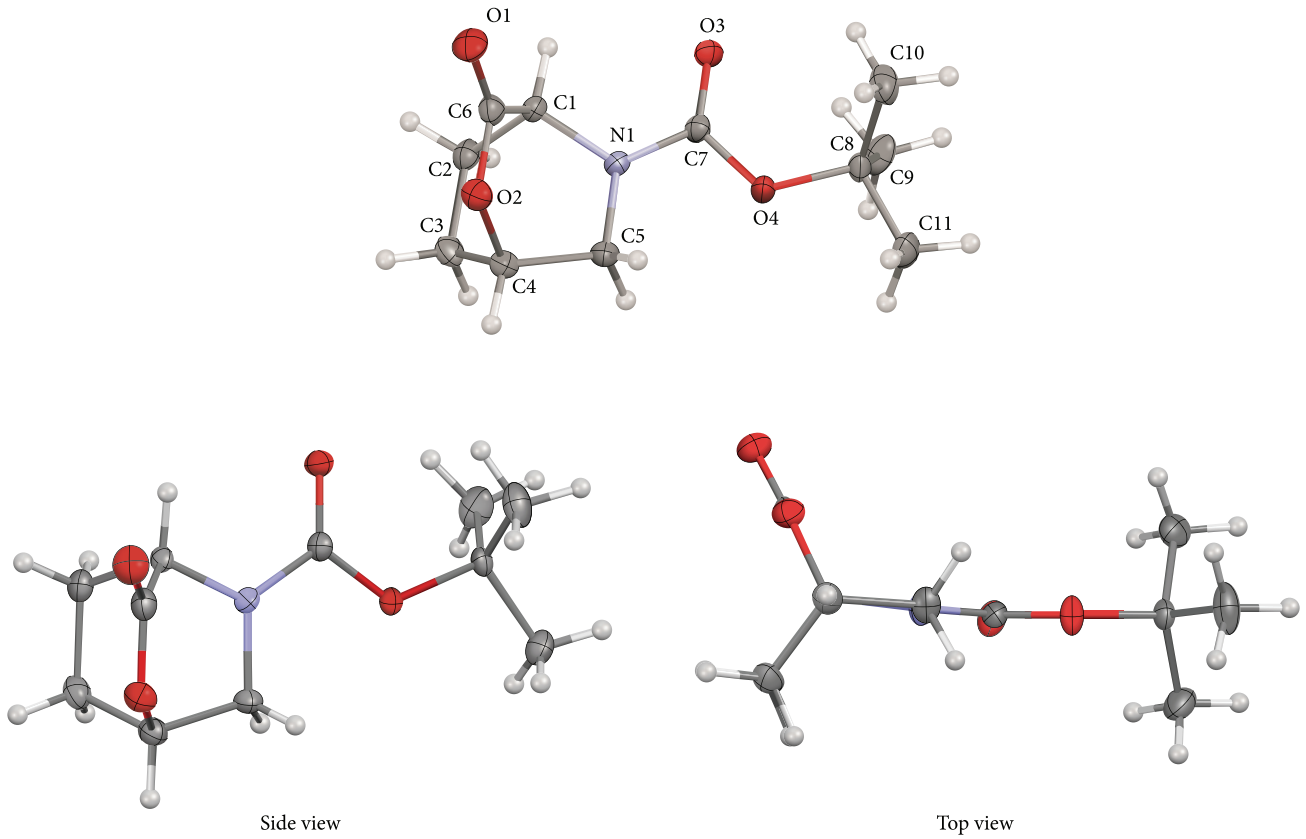


Figure 1: Molecular view of (2*S*, 5*S*)-*tert*-butyl 3-oxo-2-oxa-5-azabicyclo[2.2.2]heptane-5-carboxylate. One of two isomers is only shown (below, side, and top views). Displacement ellipsoids are drawn at the 50% probability level. The blue and red ellipsoids represent N and O atoms, respectively.

variables.), and the unit weights were used in the LS calculation (least-squares function minimized: (SHELXL-2013): $\Sigma w(F_o^2 - F_c^2)^2$ where w = least-squares weights.).

The maximum and minimum peaks on the final difference Fourier map corresponded to 0.158 and −0.126 eÅ^{-3} with an RMS deviation of 0.04 e/Å^3, respectively.

In the CIF data, no "Alert A, B, and C" appeared in the On-line Check Report from the Cambridge Crystal Data Centre (CCDC).

Atomic coordinates, displacement parameters, bond lengths, and bond angles are summarized in the Additional Information.

3. Results and Discussion

3.1. Synthesis of (2S, 5S)-tert-Butyl 3-Oxo-2-oxa-5-azabicyclo[2.2.2]octane-5-carboxylate (Scheme 1). The 5-hydroxypipecolic acid derivative chiral(2*S*, 5*S*)-*tert*-butyl 3-oxo-2-oxa-5-aza-bicyclo[2.2.2]octane-5-carboxylate was synthesized from a diastereomeric mixture of *tert*-butoxycarbonyl-*l*-5-hydroxypipecolic acid benzyl ester. In this reaction, only the *cis* isomer underwent lactonization to form the desired bicyclo[2.2.2]octane product. The remaining *trans* isomer was readily removed from the reaction mixture by washing of the organic layer with an alkaline solution (4% $NaHCO_3$). Because the lactone is less polar than the trans-5-hydroxypipecolic acid derivative, the lactone was readily isolated without the need for chiral column chromatography.

3.2. Characterization of (2S, 5S)-tert-Butyl 3-Oxo-2-oxa-5-azabicyclo[2.2.2]octane-5-carboxylate. In the high-resolution mass spectrum of the lactone, only two intensive signals with characteristic isotopic patterns for $[M + H]^+$ and $[M + Na]^+$ were detected. In addition, in the ^{1}H NMR spectrum, only several multiplets of proton signals corresponding to the methylene groups of the azabicyclo[2.2.2]octane ring were observed. Therefore, it was quite difficult to determine the exact structure of the molecule via simple ^{1}H NMR analysis.

A single-crystal X-ray diffraction study was thus performed to determine the absolute structure of the compound.

To the best of our knowledge, the exact structure and crystal packing of this chiral lactone compound have not been previously characterized by X-ray analysis.

The compound crystallizes in the chiral space group $P2_12_12_1$ (No. 19) with only the (2*S*, 5*S*) diastereomer in the unit cell (Z = 4, Figure 1). No intra- and intermolecular hydrogen bonds exist in the crystal, but some intermolecular short contacts appear. In addition, no solvent molecules are included in the crystals. The N1 nitrogen atom is located on the azabicyclo[2.2.2]octane ring, and the local conformation

Table 1: Crystallographic data for (2*S*, 5*S*)-*tert*-butyl 3-oxo-2-oxa-5-azabicyclo[2.2.2]-heptane-5-carboxylate.

Empirical formula	$C_{11}H_{17}N_1O_4$	
Formula weight	227.26	
Temperature	90 K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$ (no. 19)	
Unit cell dimensions	$a = 9.6453(10)$ Å	$\alpha = 90^\circ$
	$b = 9.7077(10)$ Å	$\beta = 90^\circ$
	$c = 12.2221(12)$ Å	$\gamma = 90^\circ$
Volume	1144.4(2) Å^3	
Z	4	
Density (calculated)	1.319 g/cm^3	
Absorption coefficient	0.100 mm^{-1}	
$F(000)$	489	
Crystal size	0.300 × 0.300 × 0.200 mm	
Theta range for data collection	2.68 to 25.00°	
Index ranges	$-11 \le h \le 11$, $-11 \le k \le 11$, $-14 \le l \le 14$	
Reflections collected	11171	
Independent reflections	2035 [R(int) = 0.0216]	
Reflections [$I > 2$sigma(I)]	2035	
Completeness to theta = 25.00°	100.0%	
Absorption correction	Empirical	
Refinement method	Full-matrix least-squares on F^2	
Data/restraints/parameters	2035/0/149	
Goodness-of-fit on F^2	1.038	
Final R_1 indices [$I >$ 2sigma(I)]	$R_1 = 0.0242$, $wR_2 = 0.0597$	
wR_2 indices (all data)	$R_1 = 0.0249$, $wR_2 = 0.0601$	
Absolute structure parameter	0.0(5)	
Largest diff. peak and hole	0.158 and −0.126 eÅ^{-3}	

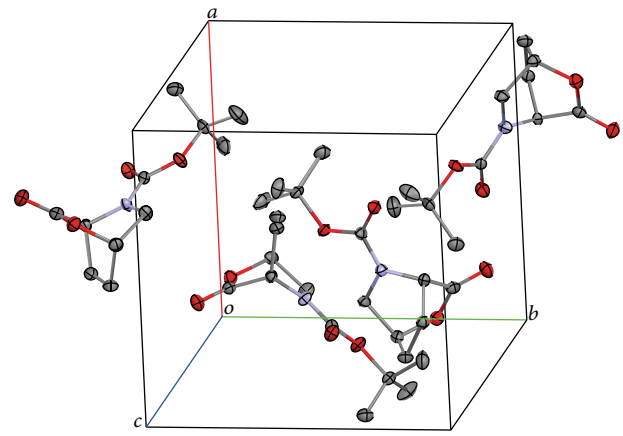


Figure 2: Crystal packing of (2*S*, 5*S*)-*tert*-butyl 3-oxo-2-oxa-5-azabicyclo[2.2.2]heptane-5-carboxylate. The blue and red ellipsoids represent N and O atoms, respectively. All hydrogen atoms are omitted for clarity.

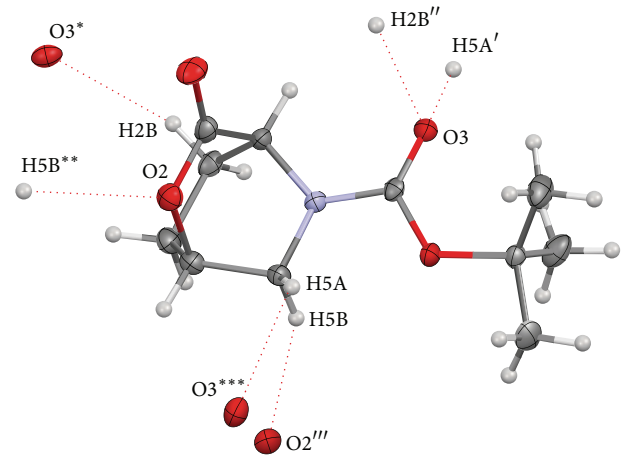


Figure 3: Intermolecular short contacts in (2*S*, 5*S*)-*tert*-butyl 3-oxo-2-oxa-5-azabicyclo[2.2.2]heptane-5-carboxylate. The blue and red ellipsoids represent N and O atoms, respectively.

of the piperidine ring on the azabicyclo[2.2.2]octane moiety is fixed exactly in the boat form by the lactone bridge linking the 2- and 4-positions of the piperidine ring. Interestingly, only suitable single crystals for X-ray structure analysis were obtained for the chiral *S*, *S* isomer of the product (Figure 3). No (*S*, *R*) and (*R*, *S*) isomers were obtained due to the structural properties of the molecule.

Table 2 lists selected bond lengths (Å) and bond angles (°) for the compound. Notably, the N1 atom on the bicyclo[2.2.2]octane ring is not located on the stem of the piperidine ring with the boat conformation.

In addition, the shorter bond length of the N1–C7 bond (1.3561(16) Å) is due to the effect of the π-conjugation of the C7–O3 double bond on the lone pair of N1. Furthermore, the bond lengths of the C–C single bonds in the bicyclo[2.2.2]octane framework are normal values at approximately 1.53 Å (Table 2).

The bicyclo[2.2.2]octane structure is slightly strained in the crystal lattice, which can be attributed to the differences in the distances of the three ring bridges (C1–N1–C5–C4, C1–C6–O2–C4, and C1–C2–C3–C4). In the bicyclo[2.2.2]octane ring plane, the dihedral angles between C1–N1–C5–C4 and C1–C6–O2–C4, C1–C6–O2–C4 and C1–C2–C3–C4 and C1–N1–C5–C4 and C1–C2–C3–C4 are 60.24°, 61.46°, and 58.31°, respectively. Lechner et al. reported the X-ray analysis of *tert*-butyl 3-oxo-2-oxa-5-azabicyclo[2.2.1]heptane-5-carboxylate [13]. The molecular structure of the azabicyclo[2.2.1] compound was highly strained due to the presence of a five-membered pyrrolidine ring moiety. Although the present lactone with a bicyclo[2.2.2] moiety is slightly strained, the distortion degree is very small compared to that of the azabicyclo[2.2.1] compound.

Table 2: Selected bond lengths (Å) and bond angles (°) in (2*S*, 5*S*)-*tert*-butyl 3-oxo-2-oxa-5-azabicyclo[2.2.2]heptane-5-carboxylate.

O1–C6	1.2005(15)	O2–C6	1.3543(15)
O2–C4	1.4709(16)	O3–C7	1.2148(15)
O4–C7	1.3448(15)	O4–C8	1.4779(15)
N1–C1	1.4639(15)	N1–C5	1.4669(16)
N1–C7	1.3561(16)	C1–C2	1.5325(18)
C2–C3	1.5439(19)	C3–C4	1.5163(19)
C4–C5	1.5096(18)	C6–C1	1.5162(17)
C8–C9	1.5112(19)	C8–C10	1.5091(19)
C8–C11	1.5128(19)		
N1–C1–C2	109.75(10)	O4–C8–C11	101.95(10)
N1–C1–C6	107.12(10)	C1–N1–C5	114.67(10)
N1–C5–C4	105.82(10)	C1–N1–C7	121.40(11)
O1–C6–O2	120.85(12)	C1–C2–C3	107.47(10)
O1–C6–C1	127.09(12)	C2–C1–C6	106.63(11)
O2–C6–C1	112.03(10)	C2–C3–C4	108.86(10)
O2–C4–C5	107.48(10)	C3–C4–C5	112.49(11)
O2–C4–C3	108.30(10)	C4–O2–C6	112.83(10)
O3–C7–O4	126.49(11)	C5–N1–C7	123.80(11)
O3–C7–N1	124.32(12)	C7–O4–C8	120.85(10)
O4–C7–N1	109.19(11)	C9–C8–C10	112.51(12)
O4–C8–C9	110.55(10)	C9–C8–C11	111.19(12)
O4–C8–C10	109.79(11)	C10–C8–C11	110.36(11)

Table 3: Intermolecular short contacts (Å) in the crystal of (2*S*, 5*S*)-*tert*-butyl 3-oxo-2-oxa-5-azabicyclo[2.2.2]heptane-5-carboxylate.

O2–H5B**	2.510	H2B–O3*	2.487
O3–H5A$'$	2.662	H5A–O3***	2.662
O3–H2B$''$	2.487	H5B–O2$'''$	2.510

We previously reported the dihedral angles for the bicyclo[2.2.2]octane ring planes of "racemic" *tert*-butyl 3-oxo-2-oxa-5-azabicyclo[2.2.2]octane-5-carboxylate [8]. A comparison of the present results with the former data revealed differences in the dihedral angles. Notably, the corresponding dihedral angles for the "racemic" crystal were 60.33°, 61.55°, and 58.16°, respectively. The slight differences in the dihedral angles can be explained not only by the greater length of the lactone bridge compared to that of the piperidine ring bridge, but also by the differences in the crystal packing (Figure 2).

In addition, the C=O double bond length on the azabicyclo[2.2.2]octane moiety was 1.2005(15) Å, while the C=O double bond length in the Boc group was 1.2148(15) Å. This difference is attributed to both the influence of the π-conjugated system including the O3 and N1 atoms and the effect of the intermolecular short contacts in the chiral crystal, which are depicted in Figure 3 and listed in Table 3. Notably, the number of short contacts in the present crystal was fewer (6) than that (14) in the "racemic" crystal [8], and the Boc groups did not form intermolecular short contacts with the neighbor molecules.

4. Conclusions

The chiral lactone (2*S*, 5*S*)-*tert*-butyl 3-oxo-2-oxa-5-azabicyclo[2.2.2]octane-5-carboxylate as a natural cyclic amino acid ester consisting of a lactone and a piperidine group was synthesized and characterized by ^{1}H NMR spectroscopy, pos. FAB-MS, and high-resolution MS. The exact structure was also determined via single crystal X-ray diffraction analysis. Only the (2*S*, 5*S*) diastereomer of the compound was included in the noncentrosymmetric unit cell, and no solvent molecules were present.

Additional Information

CCDC no. 1020363 contains the supplementary crystallographic data for the compound (2*S*, 5*S*)-*tert*-butyl 3-oxo-2-oxa-5-azabicyclo[2.2.2]octane-5-carboxylate. The data can be obtained free of charge via https://www.ccdc.cam.ac.uk/data_request/cif by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallography Data Centre, 12 Union Road, Cambridge, CB2 IEZ, UK. Fax: +44(0) 1223-336033.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

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