ASYMMETRIC SYNTHESIS OF A HOMOCHIRAL Δ^2-ISOXAZOLINE AMINO ACID DERIVATIVE

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Abstract– (2*R*)-4-Methylene-2-phenyl-3-propionyloxazolidin-5-one underwent 1,3-dipolar cycloaddition with 2,6-dichlorobenzonitrile oxide to give (5*S*,7*R*)-3-(2,6-diphenyl)-7-phenyl-6-propionyl-2,6-diaza-1,8-dioxaspiro[4.4]non-2-en-9-one, a protected isoxazoline amino acid. The reaction proceeded regiospecifically and with high stereoselectivity. The *anti* addition product predominated. The regiochemistry of addition was determined by nmr and the stereochemistry of addition was determined by X-ray analysis. The transition state energies for *syn* and *anti* addition were calculated using the semi-empirical AM1 method in the MOPAC package.

INTRODUCTION

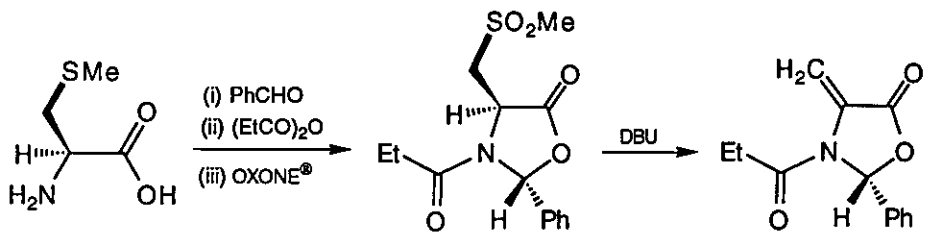
Recent interest in unnatural and non-proteinogenic α-amino acids stems from their increasing use as conformational modifiers for physiologically active peptides, and from their intrinsic biological activity.[1-3] α,β-Dehydroalaninates have been used in 1,3-dipolar cycloaddition reactions to prepare heterocyclic α-amino acids,[4] as have 4-arylidene-2-phenyl-5(4*H*)-oxazolones[5-7] and 4-arylidene-2-phenyl-5(4*H*)-thiazolones.[8] These reactions all proceeded regiospecifically but with no diastereoselectivity, thus producing racemic α-amino acid derivatives.

A stereocontrolled, Diels-Alder synthesis of carbocyclic α-amino acid derivatives was recently reported in which 2-phenyl- and 2-*t*-butyl- (2*R*)-3-benzoyl-4-methyleneoxazolidin-5-ones were

used as dienophiles.[9] Our interest in nitrile oxide cycloaddition reactions,[10] and the known biological activity of some isoxazole amino acids[11,12] and isoxazoline amino acids,[13,14] prompted us to investigate the reactivity and stereoselectivity of 2,6-dichlorobenzonitrile oxide towards (2*R*)-4-methylene-2-phenyl-3-propionyloxazolidin-5-one (**3**).

RESULTS AND DISCUSSION

(2*R*)-4-Methylene-2-phenyl-3-propionyloxazolidin-5-one (**3**) was prepared according to the method of Pyne and coworkers[9] as outlined in Scheme 1. (2*S*)-S-Methylcysteine (**1**) was condensed with benzaldehyde and then treated with propionic anhydride to give (2*R*, 4*S*)-4-(methylthiomethyl)-2-phenyl-3-propionyloxazolidin-5-one, which was oxidised with OXONE® to give the corresponding (2*R*, 4*S*)-sulphone (**2**). After the usual workup and recrystallization only a single enantiomer, the *trans* product (**2**), was present. The homochiral sulphone (**2**) was then treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to give (2*R*)-4-methylene-2-phenyl-3-propionyloxazolidin-5-one (**3**). In the procedure reported by Pyne and coworkers,[9] similar sulphones were treated with DBU for 30 min at 0°C to effect the elimination reaction. We found, in the present case, that the reaction was essentially complete within 1-2 min and that longer reaction times led to some product decomposition.



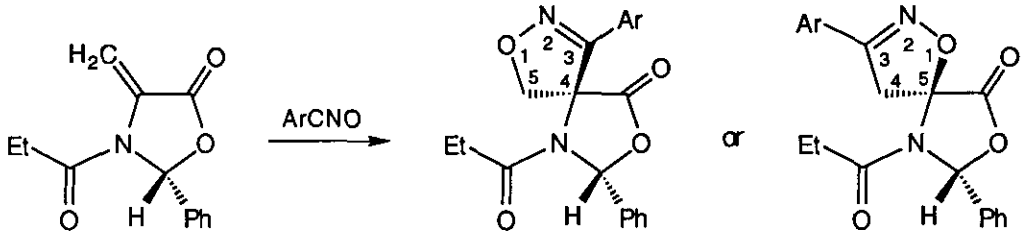
(**1**) (**2**) (**3**)

Scheme 1

In the ^{1}H nmr spectrum of **3**, one of the α-methylene protons, and the propionyl methylene proton resonances were broadened. This has been observed for similar structures.[15] Likewise, in the ^{13}C nmr spectrum of **3**, the amide carbonyl and the α-methylene carbon resonances were unusually broad. The quaternary ring carbon (C4) was broadened such that it could not be

resolved. This behaviour is presumably due to restricted inversion of the ring nitrogen (N3) or restricted rotation of the carbonyl-nitrogen bond.

2,6-Dichlorobenzonitrile oxide was generated *in situ* by dehydrohalogenation of 2,6-dichlorobenzohydroximinoyl chloride[16] with triethylamine. (2*R*)-4-Methylene-2-phenyl-3-propionyloxazolidin-5-one **(3)** reacted smoothly with the nitrile oxide to give essentially a single cycloaddition adduct, as evidenced by the ^{1}H and ^{13}C nmr spectra of the crude product mixture. The formation of regioisomer **(4)** is unlikely since the nitrile oxide oxygen atom usually becomes bonded to the more hindered olefinic site regardless of activating groups.[17] Examination of the ^{1}H nmr spectrum of the purified adduct further supported that the regioisomer formed was **5**. The magnetically non-equivalent methylene protons of the Δ^2-isoxazoline ring were situated at 3.8–3.9 ppm. The reported range for protons attached to C5 of the Δ^2-isoxazoline ring is 4.5–5.0 ppm and the reported range for protons attached to C4 of the Δ^2-isoxazoline ring is 2.8–3.8 ppm.[18] As the observed resonances fall closer to the latter range, and are likely to be shifted downfield by the adjacent amide moiety, we assigned the structure such that the spiro link is at position 5 of the Δ^2-isoxazoline ring, as in **5**.



(3) **(4)** **(5)**

Furthermore, since only one diasteroisomeric adduct was detected, it was postulated that the nitrile oxide added from the face opposite to the phenyl substituent leading to an *S* configuration at the spiro link. An X-ray crystallographic analysis of **5** confirmed the regiochemistry of addition, and the stereochemistry of the spiro linkage through the known stereochemistry of the oxazolidinone ring.

X-ray Analysis

A perspective view of the X-ray structure of **5** is shown in Figure 1 and selected dimensions are given in Table 2 (see experimental). The atoms of the isoxazoline ring are coplanar to within

experimental limits and the phenyl ring at C3 is nearly orthogonal to it, the interplanar angle being 94.3(4)°. The oxazolidinone ring atoms are coplanar to within 0.06(1) Å, with O9 lying 0.09(1) Å from the plane, and the interplanar angle between the ring and the associated phenyl ring at C7 is 60.2(3)°. The orientation of the N-propionyl group to the oxazolidinone ring is given by the torsion angles C7-N6-C1"-O1" -7.2(5)°, C5-N6-C1"-C2" +22.9(6)° and N6-C1"-C2"-C3" +178.5(4)°.

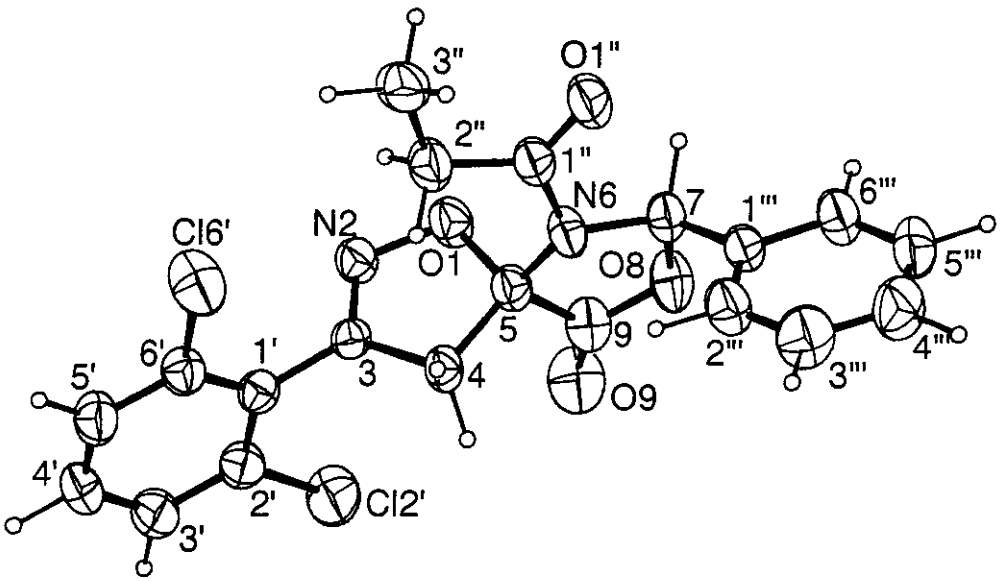


Figure 1. ORTEP drawing of **5** with thermal ellipsoids scaled to the 50% probability level and hydrogen atoms shown as spheres of arbitrary radii.

The bond lengths and angles in **5** correspond well to those of comparable structures. The O1-N2 bond length is 1.415(4) Å, and the N2-C3 bond of 1.270(5) Å is typical for a C=N bond. The two N-C bond lengths in the oxazolidinone ring are significantly different, being 1.471(4) and 1.433(5) Å for N6-C7 and N6-C5 respectively, and the two C-O bonds, in the ring show the usual asymmetry typical of such systems, in this case differing by *ca.* 0.07 Å.

Transition State Analysis

The heats of formation for **5** and the corresponding 5*R* diasteroisomer (*anti* and *syn* addition products, respectively) were calculated using the semi-empirical AM1 Hamiltonian[19,20] in the

MOPAC package. Both molecules were completely optimised and the MMOK keyword was specified to apply the molecular mechanics correction for amide linkages. The heats of formation differed by less than 1 kcal/mol, with the *anti* adduct **(5)** being more stable than the *syn* addition product (-25.5 kcal/mol and -24.6 kcal/mol, respectively). However, since the cycloaddition reaction is not a thermodynamic equilibrium the relative stabilities of the products is of less interest than the energies of the corresponding transition states.

The transition state geometry for 1,3-dipolar cycloaddition between fulminic acid (HCNO) and ethylene, using *ab initio* multiconfiguration self-consistent-field calculations with the standard STO-3G and 4-31G basis sets, has been reported.[21] To calculate the transition state energies in the present work the five atoms involved in the cycloaddition were fixed in the reported transition state geometry and the remainder of the molecule, for both *syn* and *anti* addition, was optimised using AM1. This method has the advantage of using an *ab initio* calculated transition state geometry for the atoms involved in the cycloaddition while making use of less computationally intensive semi-empirical methods to determine the heats of formation. The transition state for *anti* addition, leading to **5**, was calculated to have a heat of formation of 32.1 kcal/mol while the transition state energy for *syn* addition was 34.1 kcal/mol. This suggests that the two processes are close enough in energy to be competitive but that the *anti* addition path will be preferred, as was observed experimentally.

EXPERIMENTAL

General: Melting points were taken in open capillary tubes and are uncorrected. ^{1}H and ^{13}C nmr spectra were recorded at 200 MHz and 50 MHz, respectively, at room temperature. Solute concentrations were 50-100 mg/ml in 5 mm tubes. Infrared spectra were recorded in Nujol mulls. Chemical ionization (CI) mass spectra were obtained on a JEOL JMS-DX303 instrument, using methane as the reagent gas. Commercially available solvents and reagents were used without further purification, and light petroleum refers to a fraction of bp 60-80°C. Merck silica gel 60 (0.040-0.063 mm) was used for flash chromatography. Molecular modeling was carried out using ChemX as an interface to the MOPAC package on a Silicon Graphics IRIS Workstation.

(2*R*, 4*S*)-4-(Methylthiomethyl)-2-phenyl-3-propionyloxazolidin-5-one. A solution of (2*S*)-S-methylcysteine (6 g, 44 mmol) and sodium hydroxide (1.77 g, 44 mmol) in water (25 ml) was evaporated to dryness and the resulting solid crushed to a fine powder. Petroleum spirit (80 ml) and benzaldehyde (5.65 ml, 0.53 mol) were added and the mixture heated at reflux for 8 h with azeotropic removal of water. After evaporation to dryness, the residue was taken up in dichloromethane (50 ml) and propionic anhydride (5.77 g, 44 mmol) added dropwise under a nitrogen atmosphere at 0°C. The mixture was stirred for 2 days at room temperature; sodium carbonate (10 g) was added and the mixture stirred for a further 2 h. Excess sodium carbonate was removed by filtration and the concentrated filtrate was diluted with ether (50 ml). The resulting precipitate was collected and washed with diethyl ether. Recrystallisation (ether) afforded colourless crystals (7.6 g, 61%); mp 116°C; ν_{max} 1800, 1660 cm^{-1}; $[\alpha]_D^{23}$ = +210.4° (c, 1.0 in CH_2Cl_2); ^1H nmr (200 MHz, $CDCl_3$) δ 0.91 (t, J=7.3 Hz, 3H, $CH_2C\underline{H}_3$), 1.57-1.80 (m, 1H, $C\underline{H}_2CH_3$), 1.94-2.12 (m, 1H, $C\underline{H}_2CH_3$), 2.17 (s, 3H, SCH_3), 3.05 (dd, J=1.55, 14.26 Hz, 1H, CH_2S), 3.86 (dd, J=4.22, 14.26 Hz, 1H, CH_2S), 4.90-5.01 (b, 1H, H4), 6.64 (s, 1H, H2), 7.31-7.53 (m, 5H, Phenyl); ^{13}C nmr (50 MHz, $CDCl_3$) δ 10.4 ($CH_2\underline{C}H_3$), 19.1 (CH_3S), 30.6 ($\underline{C}H_2CH_3$), 36.0 (CH_2S), 59.8 (C4), 93.1 (C2), 128.9 (*m*-Ph), 131.5 (*o*-Ph), 132.9 (*p*-Ph), 138.5 (*ipso*-Ph), 172.6 (C=O), 173.9 (C=O); found: MH^+ 280.0997, $C_{14}H_{18}NO_3S$ requires: MH^+ 280.1007; *m/z* 280 (12), 252 (15), 224 (100), 174 (16), 146 (15).

(2*R*, 4*S*)-4-(Methylsulfonylmethyl)-2-phenyl-3-propionyloxazolidin-5-one (2). A solution of OXONE® (5.0 g) and (2*R*, 4*S*)-4-(methylthiomethyl)-2-phenyl-3-propionyloxazolidin-5-one (3.8 g, 13.6 mmol) in water (150 ml) and acetonitrile (20 ml) was stirred for 8 h at room temperature. The mixture was filtered and the filtrate extracted with dichloromethane (5 x 100 ml). The combined extracts were dried ($MgSO_4$) and concentrated to give a cream precipitate which was recrystallised (dichloromethane, petroleum spirit) to give colourless crystals (4.1 g, 97%); mp 136.5-137°C (decomp); ν_{max} 1800, 1680 cm^{-1}; $[\alpha]_D^{23}$ = +164.9° (c, 1.0 in CH_2Cl_2); ^1H nmr (200 MHz, DMSO-d_6) δ 0.67 (t, J=7.2 Hz, 3H, $CH_2C\underline{H}_3$), 1.31-1.54 (m, 1H, $C\underline{H}_2CH_3$), 1.95-2.18 (m, 1H, $C\underline{H}_2CH_3$), 3.08 (s, 3H, SO_2CH_3), 3.74 (d, J=14.5 Hz, 1H, CH_2SO_2), 4.38 (dd, J=5.2, 14.5 Hz, 1H, CH_2SO_2), 5.36-5.49 (b, 1H, H4), 6.85 (s, 1H, H2), 7.40-7.74 (m, 5H, Ph); ^{13}C nmr (50 MHz, DMSO-d_6) δ 8.0 ($CH_2\underline{C}H_3$), 27.8 ($\underline{C}H_2CH_3$), 42.9 (CH_3SO_2), 50.6 (CH_2SO_2), 52.1 (C4), 89.6 (C2), 127.2 (*m*-Ph), 128.9 (*o*-

Ph), 130.3 (*p*-Ph), 136.5 (*ipso*-Ph), 169.3 (C=O), 171.3 (C=O); found: MH^+ 312.0886, $C_{14}H_{18}NO_5S$ requires: MH^+ 312.0906; *m/z* 312 (6), 284 (9), 256 (100), 206 (25), 176 (15), 57 (8).

(2*R*)-4-Methylene-2-phenyl-3-propionyloxazolidin-5-one (3). 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (7.4 ml, 4.9 mmol) was added to a solution of (2*R*, 4*S*)-4-(methylsulfonylmethyl)-2-phenyl-3-propionyloxazolidin-5-one **(2)** (1.37 g, 4.4 mmol) in dichloromethane (20 ml) at 0°C under a nitrogen atmosphere. The solution was stirred for 2–3 min at 0°C and then brine (15 ml) was added. The organic layer was separated and the aqueous layer extracted with dichloromethane (3 x 20 ml). The combined organic extracts were dried ($MgSO_4$), then passed through a short column of silica gel 60 (Merck 9385) to remove traces of unreacted DBU. The solvent was evaporated to afford a clear, colourless oil (0.98 g, 96%); ν_{max} 2975 (br), 1800, 1700 cm^{-1}; $[\alpha]_D^{23}$ = +166.5° (c, 1.0 in CH_2Cl_2); ^1H nmr (200 MHz, $CDCl_3$) δ 1.06 (t, J=7.0 Hz, 3H, CH_3), 2.22-2.56 (br, 2H, CH_2), 5.83 (*s*, 1H, C=CH_2), 6.64 (br, 1H, C=CH_2), 6.72 (s, 1H, H2), 7.3-7.5 (m, 5H, Ph); ^{13}C nmr (50 MHz, $CDCl_3$) δ 7.9 (CH_3), 29.1 (CH_2), 88.7 (C2), 103.7 (C=$\underline{C}H_2$), 126.4 (*o*-Ph), 129.3 (*m*-Ph), 130.6 (*p*-Ph), 135.6 (*ipso*-Ph), 163.8 (NC=O), 171.1 (OC=O); found: MH^+ 232.0980, $C_{13}H_{14}NO_3$ requires: MH^+ 232.0974; *m/z* 232 (10), 204 (23), 176 (100), 126 (22), 107 (37), 75 (16), 57 (43).

(5*S*, 7*R*)-3-(2,6-Dichlorophenyl)-7-phenyl-6-propionyl-2,6-diaza-1,8-dioxaspiro[4.4]non-2-en-9-one (5). A solution of 2,6-dichlorobenzohydroximinoyl chloride[16] (0.69 g, 3.1 mmol) in dichloromethane (5 ml) was added dropwise to a solution of (2*R*)-4-methylene-2-phenyl-3-propionyloxazolidin-5-one **(3)** (0.71 g, 3.1 mmol) and triethylamine (0.47 ml, 3.4 mmol) in dichloromethane (20 ml) at room temperature. The solution was stirred for 8 h. The crude reaction mixture was passed through a short column of silica gel 60 (Merck 9385) and the solvent evaporated to give an orange paste. Recrystallisation from ether afforded colourless crystals (0.89 g, 71%); mp 190.8-191.0°C; ν_{max} 1800, 1700 cm^{-1}; $[\alpha]_D^{23}$ = –10.4° (c, 1.0 in CH_2Cl_2); ^1H nmr (200 MHz, $CDCl_3$) δ 1.08 (t, J=7.0 Hz, 3H, CH_3), 2.22-2.56 (um, 2H, CH_2), 3.91 (d, J=18.0 Hz, 1H, H4), 4.08 (d, J=18.0 Hz, 1H, H4), 6.77 (s, 1H, H7), 7.21-7.51 (m, 8H, Ar); ^{13}C nmr (50 MHz, $CDCl_3$) δ 8.0 (CH_3), 28.7 (CH_2), 44.6 (C4), 89.5 (C7), 92.1 (C5), 126.2, 128.2, 129.2, 130.5, 131.7, 135.4, 135.7, 153.8 (C=N), 168.4 (C=O), 172.5 (C=O); found: MH^+ 419.0560, $C_{20}H_{17}Cl_2N_2O_4$ requires: MH^+ 419.0565; *m/z* 419 (52), 420 (34), 391 (18), 364 (37), 363 (56), 347 (23), 345 (35), 318 (14), 317 (21), 163 (16), 162 (100), 130 (48), 106 (22).

Crystallographic Analysis

Compound (5) formed colourless prismatic crystals from hexane/ethyl acetate. The setting angles for 25 reflections, $46^{\circ} < 2\theta$ (Cu Kα)$< 70^{\circ}$, were used to determine the cell parameters. Intensities were measured at 289(1) K on a Rigaku-AFC diffractometer with Cu Kα radiation (graphite-crystal monochromator, λ = 1.5418 Å). The data were recorded by an ω-2θ scan with a range ($\Delta\omega$) of $1.2^{\circ} + 0.5^{\circ}\tan\theta$ and scan rate 2° min^{-1}. Three standard reflections monitored every 50 reflections showed no significant variation in intensity during the data collection. Data to a 2θ(max) of 130° yielded 1751 unique terms. The integrated intensities were corrected for Lorentz and polarization effects and for absorption (transmission factors ranged between 0.215 and 0.443).

The structure was solved by direct methods with SHELXS86.[22] Full-matrix least-squares refinement with SHELX76[23] converged at R = 0.040, R_w = 0.062 and S = 1.08 (defined as $[\Sigma w(\Delta F)^2/N_v - N_p)]^{1/2}$ for 268 variables (N_v) and 1669 data (N_o) for which $I > 2\sigma I$. Anisotropic temperature factors were given to the non-hydrogen atoms and isotropic to the H-atoms which were included at idealised positions (C-H 1.08 Å). The function minimized was $\Sigma w(\Delta F)^2$ with $w = (\sigma^2|F_o| + 0.0035|F_o|^2)^{-1}$. Three intense low order terms (-1 1 1, -1 2 1, -1 2 2) badly affected by extinction were omitted from the final refinement. The largest peaks on the final difference map were of heights +0.28 and -0.30 e Å^{-3}, and the maximum shift-to-error ratio at convergence was 0.04:1. The atomic scattering factors used were those stored in SHELX76.

The final atomic coordinates are given in Table 1 and selected bond lengths, interbond and torsion angles are listed in Table 2. Figure 1 has been prepared from the ouput of ORTEP-II.[24] Anisotropic thermal parameters, hydrogen atom coordinates, short intermolcular contacts and listings of observed and calculated structure amplitudes are available as supplementary material.

Crystal Data for 5 .

Chemical formula , $C_{20}H_{16}Cl_2N_2O_4$; Formula weight, 419.3; Crystal system, monoclinic; Space group, $P\,2_1$; a (Å), 6.336(1); b (Å), 11.342(1); c (Å), 13.507(1); β (deg), 97.17(1); V (Å^3), 963.1(3); Z, 2; D_m (g cm^{-3}), 1.442(5); D_C (g cm^{-3}), 1.446; F(000), 432; λ (Å), 1.5418; μ (Cu Kα) (cm^{-1}), 33.34; Crystal size (mm), 0.30x0.49x0.49; T (K), 289(1).

Table 1. Fractional atomic coordinates (x10^4) and equivalent isotropic temperature factors (Å^2) for the non-H atoms with estimated standard deviations in parentheses for compound **(5)**.

$$B_{eq} = \frac{8}{3}\pi^2 \sum_i \sum_j U_{ij} a_i^* a_j^* a_i \cdot a_j$$

Atom	x	y	z	B_{eq}
O1	2986(4)	6557(0)	7084(2)	3.75(5)
N2	3779(4)	6090(3)	8029(2)	3.19(6)
C3	4888(5)	5177(4)	7917(2)	2.64(6)
C4	5018(5)	4843(4)	6844(2)	3.00(6)
C5	3617(5)	5808(4)	6300(2)	3.05(6)
N6	4372(4)	6527(4)	5545(2)	3.31(6)
C7	2736(5)	6687(4)	4682(2)	3.31(7)
O8	1057(4)	5870(4)	4886(2)	4.21(6)
C9	1522(5)	5321(5)	5756(2)	3.68(8)
O9	403(5)	4604(5)	6069(2)	5.32(7)
C1'	5771(5)	4527(4)	8821(2)	2.84(6)
C2'	4624(6)	3598(4)	9187(3)	3.44(7)
Cl2'	2219(2)	3182(3)	8537(1)	5.30(3)
C3'	5337(6)	3010(4)	10064(3)	3.99(8)
C4'	7282(6)	3346(5)	10592(2)	4.02(8)
C5'	8446(6)	4231(5)	10253(3)	4.07(8)
C6'	7697(5)	4814(4)	9373(2)	3.34(7)
Cl6'	9206(2)	5940(3)	8976(1)	5.47(3)
C1"	5889(6)	7418(4)	5682(2)	3.52(7)
O1"	5897(5)	8175(4)	5052(2)	4.84(7)
C2"	7461(6)	7390(5)	6617(3)	4.32(9)
C3"	9059(6)	8378(5)	6671(4)	4.92(10)
C1"'	3420(5)	6365(4)	3692(2)	3.28(7)
C2"'	5215(6)	5702(5)	3588(3)	4.35(9)
C3"'	5638(8)	5376(6)	2647(4)	5.62(12)
C4"'	4305(9)	5714(6)	1806(3)	5.49(11)
C5"'	2554(6)	6397(5)	1907(3)	4.99(10
C6"'	2105(6)	6728(5)	2834(3)	4.16(8)

Table 2. Bond lengths (Å), interbond and torsion angles (°) associated with the bicylic spiro moiety in **(5)** with estimated standard deviations in parentheses.

Bond Lengths (Å)		Bond Angles (°)		Torsion Angles (°)	
O1-N2	1.415(4)	N2-O1-C5	109.9(2)	O1-C5-N6-C7	-100.0(3)
N2-C3	1.270(5)	O1-N2-C3	109.7(2)	N2-O1-C5-N6	-135.2(3)
C3-C4	1.510(4)	N2-C3-C4	114.6(3)	C3-C4-C5-C9	-111.4(3)
C4-C5	1.537(5)	C3-C4-C5	100.5(2)	C4-C3-C1'-C2'	-84.4(5)
O1-C5	1.452(4)	O1-C5-C4	105.3(2)	C4-C5-C9-O8	-141.2(3)
C3-C1'	1.476(5)	O1-C5-N6	109.4(2)	C4-C5-C9-O9	+42.2(6)
C5-N6	1.433(5)	O1-C5-C9	105.0(2)	C5-N6-C1"-C2"	+22.9(6)
N6-C7	1.471(4)	C4-C5-C9	112.7(3)	N6-C1"-C2"-C3"	178.5(4)
C7-O8	1.463(5)	C4-C5-N6	121.4(3)	C7-N6-C1"-O1"	-7.2(5)
O8-C9	1.330(5)	N6-C5-C9	102.1(3)	O8-C7-C1"'-C2"'	-99.3(4)
C5-C9	1.538(5)	C5-N6-C7	111.7(3)		
C9-O9	1.190(6)	N6-C7-O8	103.2(2)		
N6-C1"	1.391(6)	C7-O8-C9	112.1(3)		
C7-C1"'	1.501(4)	C5-C9-O8	109.7(3)		

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