Synthesis of Spirolactones by 1,3-Dipolar Cycloadditions to Methyl (*S*)-3-[(*E*)-Cyanomethylidene]-2-oxotetrahydrofuran-5-carboxylate

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Dedicated to Professor Emeritus Miha Tišler on the occasion of his 75th birthday

Treatment of methyl (*S*)-5-[(*E*)-(dimethylamino)methylidene]-2-oxotetrahydrofuran-5-carboxylate (**2**) with potassium cyanide in acetic acid gave (*S*)-5-[(*E*)-cyanomethylidene]-2-oxotetrahydrofuran-5-carboxylate (**3**), which was used as chiral dipolarophile in 1,3-dipolar cycloadditions. Reactions of **3** with diazomethane (**4**) and nitrile oxides **5a–c** afforded spirolactones **6–8** in 24–34% diastereomeric excess, while with diazomethane (**4**) in the presence of triethylamine, methyl 3-cyanomethyl-2-methoxyfuran-5-carboxylate (**12**) was obtained.

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γ-Lactones are an important class of heterocyclic compounds, not only due to their synthetic utility but also because the γ-lactone structural motif is widely represented among numerous natural products and biologically active compounds [1]. Examples of spiro γ-lactones, isolated from natural sources, are bakkenolides [2,3], salvilanguidulines [4], syringolides [5], secosyrins [6], and hyperolactones [7] (Figure 1).

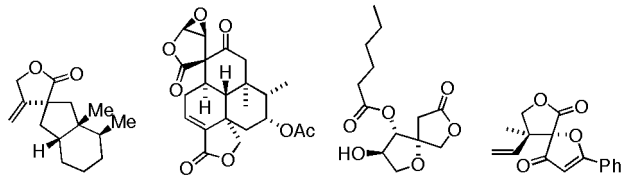


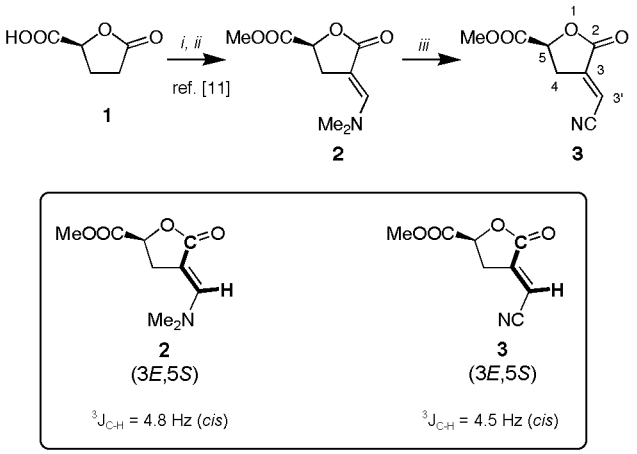
Figure 1. Some naturally occurring spiro γ-lactones.

In the course of our studies towards the synthesis of heterocyclic systems, 3-(dimethylamino)- and 3-cyanopropenoates have been employed as easily available and versatile reagents. Their chiral analogs, derived from L-pyroglutamic acid and 2-oxotetrahydrofuran-5-carboxylic acid, have been used as reagents for the preparation of optically active 3-heteroarylalanine- and 3-(heteroaryl)lactic acid derivatives and heterocyclic systems with an α-amino- or α-hydroxy acid structural element [8,9]. In this connection, we have recently reported the preparation of methyl (*S*)-1-benzoyl-3-[(*E*)-cyanomethylidene]-2-oxopyrrolidinone-5-carboxylate and its transformation into cyclic β-heteroarylalanine- and α-heteroarylglycine analogs by 1,3-dipolar cycloaddition reactions [10]. In continuation of our work in this field, we now report the preparation and cycloaddition reactions of (*S*)-5-[(*E*)-cyanomethylidene]-2-oxotetrahydrofuran-5-carboxylate (**3**).

The starting compound, methyl (*S*)-3-[(*E*)-(dimethylamino)methylidene]-2-oxotetrahydrofuran-5-carboxylate (**2**) was prepared in 2 steps from commercially available (*S*)-tetrahydrofuran-2-one-5-carboxylic acid (**1**) [11], which is also available in one step from L-glutamic acid [12]. Enaminone **2** was then treated with potassium cyanide in acetic acid at room temperature to give methyl (*S*)-5-[(*E*)-cyanomethylidene]-2-oxotetrahydrofuran-5-carboxylate (**3**) in 73% yield. The (*E*)-configuration of the exocyclic double bond in compounds **2** and **3** was determined by nmr (HMBC technique) on the basis of long-range heteronuclear coupling constants, $^3J_{C-H}$. The magnitude of coupling constants, $^3J_{C-H}$ = 4.8 and 4.5 Hz, indicates the *cis*-orientation between H–3' and C–2 (carbon atom of the ring carbonyl group) and is in agreement with the magnitudes reported in the literature. Generally, the magnitude of coupling constant $^3J_{C-H}$ for nuclei with *cis*-configuration around the C=C double bond is smaller (2–6 Hz) than that for *trans*-oriented nuclei (8–12 Hz) [10,13–15] (Scheme 1).

Compound **3**, when treated with diazomethane (**4**) and nitrile oxides **5a–c** as 1,3-dipoles, gave the corresponding spiro compounds **6–9** as cycloadducts. Thus, treatment with diazomethane (**4**) furnished optically active methyl

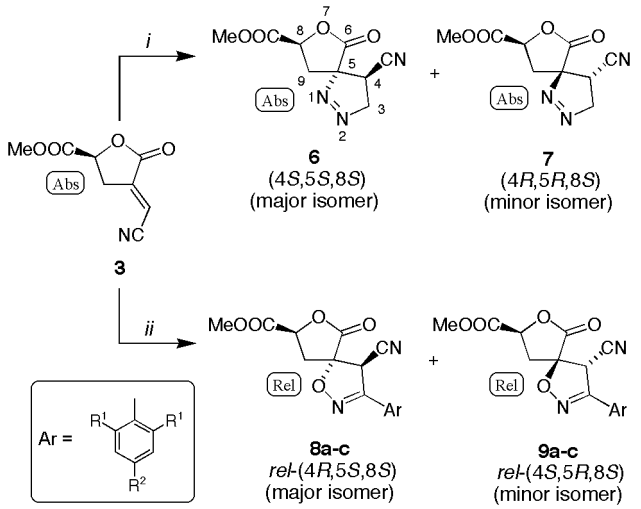
Scheme 1



Reagents and conditions: *i*) CH_2N_2 (**4**), Et_2O, 0 °C; *ii*) $Bu^tOCH(NMe_2)_2$, toluene, 100 °C; *iii*) KCN, AcOH, 20 °C.

(4*S*,5*S*,8*S*)-4-cyano-6-oxo-7-oxa-1,2-diaza[4.4]non-1-ene-8-carboxylate (**6**) and its (4*R*,5*R*,8*S*)-isomer (**7**) in a ratio of 62:38, respectively. Upon chromatographic separation, isomerically and analytically pure compounds **6** and **7** were obtained. On the other hand, reactions of **3** with nitrile oxides **5a–c** in chloroform under reflux afforded racemic methyl *rel*-(4*R*,5*S*,8*S*)-3-aryl-4-cyano-6-oxo-1,7-dioxa-2-aza[4.4]non-2-ene-8-carboxylates **8a–c** and their *rel*-(4*S*,5*R*,8*S*)-isomers **9a–c** in a ratio of 2:1, respectively. In this case, only the major isomers **8a–c** were obtained in isomerically and analytically pure form (Scheme 2).

Scheme 2



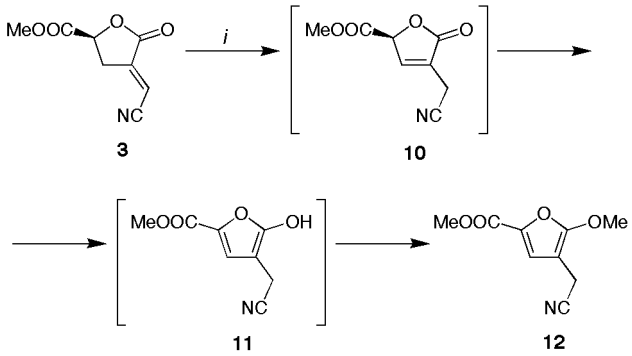
Compounds	R^1	R^2	**6** : **7** or **8** : **9**	D.e. [%]	Yield [%] **6** or **8**	**7**
6/**7**			62 : 38	24	43	24
5a, **8a**/**9a**	Me	Me	66 : 34	32	27	
5b, **8b**/**9b**	MeO	MeO	67 : 33	34	25	
5c, **8c**/**9c**	Cl	H	67 : 33	34	48	

Reagents and conditions: *i*) CH_2N_2 (**4**), Et_2O, CH_2Cl_2, –10°C, then chromatographic separation; *ii*) benzonitrile oxide (**5a–c**), $CHCl_3$, reflux, then chromatographic separation.

Since closely related cycloadditions to methyl (*S*)-1-benzoyl-3-[(*E*)-cyanomethylidene]-2-oxopyrrolidin-5-carboxylate, carried out in the presence of a base, gave fused pyrrolidinones instead of spiro compounds [10], we also performed the above mentioned cycloadditions in the presence of triethylamine. Unfortunately, analogous cycloadditions of **3** to nitrile oxides **5a–c** furnished only unseparable tarry mixtures of products. However, treatment of **3** with diazomethane (**4**) in the presence of triethylamine gave methyl 3-cyanomethyl-2-methoxyfuran-5-carboxylate (**12**). Formation of **12** might be explained by a base-catalyzed isomerization into intermediate **10** followed by aromatization into 2-hydroxyfuran derivative **11**, which is then methylated with diazomethane (**4**) (Scheme 3).

In all cases, the cycloadditions proceeded regiospecifically and in agreement with regiochemistry of analogous cycloadditions [10,16–20]. Poor stereoselectivity of cycloadditions (24–34% diastereomeric excess) was somehow expected and was most probably due to a large distance between the stereodirecting center at 5-position and the exocyclic C=C double bond. Similar stereoselectivity has been observed previously by analogous cycloadditions in 2-pyrrolidinone series. To our surprise, racemization took place upon treatment of **3** with nitrile oxides **5a–c** under essentially neutral conditions. At this moment, we do not have a firm explanation for racemization, especially since cycloaddition of 2,4,6-trimethoxybenzonitrile oxide (**5b**) to closely related methyl (*S*)-1-benzoyl-3-[(*E*)-cyanomethylidene]pyrrolidin-2-one-5-carboxylate afforded optically active spiro pyrrolidinone [10] (Scheme 2). However, formation of racemic spiro compounds **8**, **9** might be explained by initial racemization of the dipolarophile **3** *via* tautomeric equilibrium between its isomeric forms **10** and **11** (Scheme 3).

Scheme 3



Reagents and conditions: *i*) CH_2N_2 (**4**), Et_2O, CH_2Cl_2, Et_3N, 20 °C.

Structures of novel compounds **6**–**8**, **12** were determined by spectroscopic methods (ir, ^{1}H- and ^{13}C nmr) and by analyses for C, H, and N. The structures of cycloadducts **6**, **7**, **8a,c** were also determined by X-ray diffraction which also offered an additional proof for the configuration of the exocyclic C=C bond in the dipolarophile **3** (Figures 2–5).

Cycloadditions of diazomethane (**4**) and nitrile oxides **5a–c** to methyl (*S*)-3-[(*E*)-cyanomethylidene]-2-oxotetrahydrofuran-5-carboxylate (**3**) showed that spiro γ-lactones, such as 7-oxa-1,2-diazaspiro[4.4]non-1-ene- (**6**, **7**) and 1,7-dioxa-2-azaspiro[4.4]non-2-ene derivatives (**8a–c**), can be prepared regioselectively in one step from easily available dipolarophile **3**. Due to generally poor diastereoselectivity and racemization, which took place upon cycloadditions of nitrile oxides **5** to the dipolarophile **3**, further studies in this field will be focused towards stereochemical and separation issues.

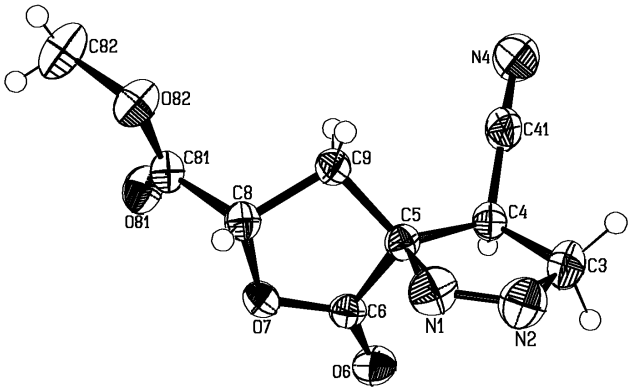


Figure 2. Ortep view of compound **6** at the 50% probability level. H atoms are drawn as circles of arbitrary radii.

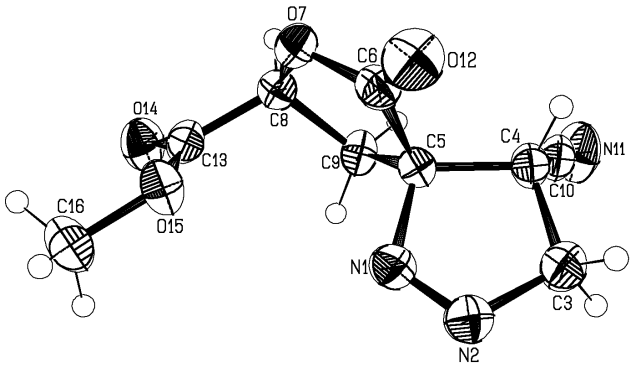


Figure 3. Ortep view of compound **7** at the 50% probability level. H atoms are drawn as circles of arbitrary radii.

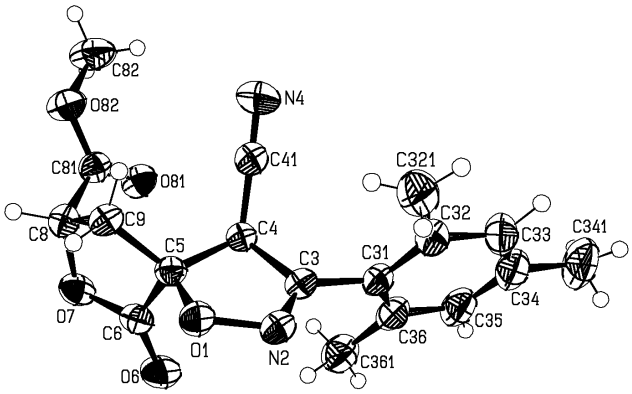


Figure 4. Ortep view of compound **8a** at the 50% probability level. H atoms are drawn as circles of arbitrary radii.

EXPERIMENTAL

All starting materials were commercially available (in most cases from Fluka AG) and purified following the standard techniques. Column chromatography: silica gel, silica gel 60, 0.04–0.06 mm (Fluka). Medium pressure liquid chromatography: Büchi isocratic system with detection [21], silica gel 60, 0.015–0.035 mm (Merck); column dimensions (dry filled): 15 x 460 mm; backpressure: 10–15 bar; detection: UV 254 nm; sample amount: 100–150 mg of isomeric mixture per each run. Tlc: alu foils coated with silica gel 60 F 254, 0.2mm (Merck). Mp: Kofler micro hot stage. Optical rotations: Perkin-Elmer 241 MC polarimeter. ^{1}H nmr (300 MHz), ^{13}C nmr (75.5 MHz), and 2D HMBC spectra: Bruker Avance DPX 300 spectrometer with deuteriochloroform and dimethyl sulfoxide–d_6 as solvents and tetramethylsilane as internal standard. Ir: Perkin-Elmer Spectrum BX FTIR spectrometer (KBr). Ms: Autospeck Q (VG-Analytical) spectrometer. Elemental analyses for C, H, and N: Perkin-Elmer CHN Analyser 2400.

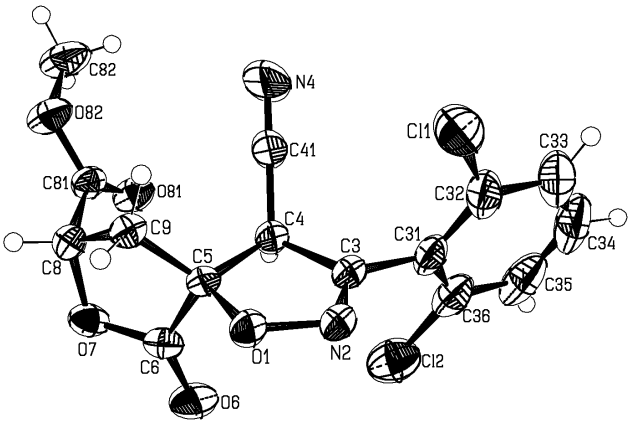


Figure 5. Ortep view of compound **8c** at the 50% probability level. H atoms are drawn as circles of arbitrary radii.

Diastereomeric excess of major isomers **6**, **8a–c** were determined by taking ^{1}H nmr spectra of crude isomeric mixtures.

The following compounds were prepared according to the procedures described in the literature: methyl (*S*)-3-[(*E*)-(dimethylamino)methylidene]-2-oxotetrahydrofuran-5-carboxylate (**2**) [11], diazomethane (**4**) [22], and benzonitrile oxides (**5a–c**) [23].

Methyl (*S*)-3-[(*E*)-Cyanomethylidene)]-2-oxotetrahydrofuran-5-carboxylate (**3**).

Potassium cyanide (0.254 g, 3.9 mmoles) was dissolved in a solution of **2** (0.597 g, 3 mmoles) in acetic acid (100%, 20 ml) and the solution was left at room temperature for 4 days. The reaction mixture was evaporated *in vacuo* to 1/4 of the initial volume (~5 ml), water (50 ml) was added, and the product was extracted with diethyl ether (4 x 50 ml). Organic phases were combined, dried over anhydrous sodium sulfate, filtered, and the filtrate was evaporated *in vacuo*. The residue was purified by column chromatography (ethyl acetate). Fractions containing the product were combined and evaporated *in vacuo* to give **3** which was used for further transformations without purification. Yield: 0.396 g (73%), colorless oil. $[\alpha]_D^{21}$ = +89.7° (c = 1.04, dichloromethane). Ir (cm^{-1}): 2230 (C≡N), 1760 (C=O). ^{1}H nmr (deuteriochloroform): δ 3.32 (1H, ddd, J = 3.0, 4.1, 19.6 Hz, 4–Ha); 3.51 (1H, ddd, J = 3.4, 9.0, 19.6 Hz, 4–Hb); 3.86 (3H, s, OMe); 5.11 (1H, dd, J = 4.1, 9.0 Hz, 5–H); 6.40 (1H, dd, J = 3.0, 3.4 Hz, 3'–H). ^{13}C nmr (deuteriochloroform): δ 31.9, 53.7, 73.5, 105.9, 115.0, 145.6, 166.5, 169.2.

Anal. Calcd. for $C_8H_7NO_4$ (181.15): C, 53.04; H, 3.89; N, 7.73. Found: C, 52.71; H, 3.96; N, 7.45. *Hrms* Calcd. for $C_8H_7NO_4$: 181.037508. Found: 181.038100.

Table 1

Crystal Data, Data Collection, and Refinement Data for Compounds **6**, **7**, **8a**, and **8c**

	6	**7**	**8a**	**8c**
Crystal data				
Chemical formula	$C_9H_9N_3O_4$	$C_9H_9N_3O_4$	$C_{18}H_{18}N_2O_5$	$C_{15}H_{10}Cl_2N_2O_5$
M_r	223.188	223.188	342.351	369.16
Cell seting	Monoclinic	Orthorhombic	Monoclinic	Monoclinic
Space group	$P2_1/n$	$P2_12_12_1$	$P2_1/c$	$P2_1/c$
a (Å)	9.3493(9)	5.4504(3)	16.462(3)	15.057(3)
b (Å)	11.410(1)	10.2657(5)	10.251(1)	10.125(8)
c (Å)	10.397(1)	17.325(1)	10.681(2)	10.665(2)
b (°)	112.836(7)	/	101.89(1)	102.04(1)
V (Å^3)	1022.2(2)	969.36(9)	1763.8(5)	1590(1)
Z	4	4	4	4
D_x (Mg m^{-3})	1.450	1.529	1.289	1.542
Radiation type	Mo *Ka*	Mo *Ka*	Mo *Ka*	Mo *Ka*
No. of reflect. for cell parameters	75	6723 [a]	100	75
θ range (°)	8.36–17.34	1.02–26.02 [a]	9.13–17.71	10.13–14.47
m (mm^{-1})	0.1166	0.1230	0.0952	0.4368
Temperature (K)	293(1)	293(1)	293(1)	293(1)
Crystal form, color	Block, colorless	Plate, colorless	Plate, colorless	Plate, colorless
Crystal size (mm)	0.64x0.57x0.53	0.20x0.10x0.05	1.29x0.80x0.10	1.07x0.65x0.25
Data collection				
Diffractometer	Nonius CAD-4	Nonius Kappa CCD	Nonius CAD-4	Nonius CAD-4
Profile data scans	*w - 2q*	*ϕ and ω*	*w - 2q*	*w - 2q*
Absorption corr.	none	none	none	none
Measured reflect.	9920	6723	17042	15442
Independent refl.	2459	1130	4235	3830
Observed refl.	1960	967	2690	2780
Criterion for obs. reflections	$I > 2.5s(I)$	$F^2 > 1.5s(F^2)$	$I > 2.5s(I)$	$I > 2.5s(I)$
R_{int}	0.0110	0.061	0.0437	0.0148
q_{max} (°)	27.95	26.02	27.93	27.97
Range of *h, k, l*	–12 →*h*→ 12	–6 →*h*→ 6	–21 →*h*→ 21	–19 →*h*→ 19
	–15 →*k*→ 15	–12 →*h*→ 12	–13 →*k*→ 13	–13 →*k*→ 13
	–13 →*l*→ 13	–21 →*h*→ 21	–14 →*l*→ 14	–14 →*l*→ 14
3 Standard refl. frequency (min)	333	/ [b]	333	333
Intens. decay (%)	1.03	/ [b]	1.77	4.86
Refinement				
Refinement on	*F*	*F*	*F*	*F*
R	0.040	0.043	0.058	0.046
wR	0.045	0.048	0.068	0.057
S	1.001	1.085	1.001	0.972
No. of refl. used in refinement	1960	967	2690	2780
No. of parameters	172	181	280	247
Weighting scheme	empirical	Regina [26]	empirical	empirical
$(\Delta/\sigma)_{max}$	0.0549	0.0114	0.1349	0.00079
$(\Delta/\sigma)_{aver}$	0.00203	0.00094	0.0042	0.000042
$\Delta\rho_{max}$ (e Å^{-3})	0.343	0.210	0.468	0.659
$\Delta\rho_{min}$ (e Å^{-3})	–0.308	–0.210	–0.431	–0.480

[a] The unit cell was determined during the image integration procedure; [b] These values are not applicable for the CCD diffractometer.

Preparation of Methyl (4*S*,5*S*,8*S*)-4-Cyano-6-oxo-7-oxa-1,2-diazaspiro-[4.4]non-1-ene-8-carboxylate (**6**) and Its (4*R*,5*R*,8*S*)-Isomer (**7**).

A cold solution (0–5°) of diazomethane (**4**) in diethyl ether (~0.4 *M*, 12 ml, ~5 mmoles) was added to a solution of **3** (0.181g, 1 mmol) in dichloromethane (5 ml) at –10° and the solution was left at –10° for 12 h. Volatile components were left to evaporate in a ventilated hood and the residue was purified by column chromatography (ethyl acetate). Fractions containing the products were combined and volatile components were evaporated *in vacuo* to give a mixture **6** and **7** which were separated by medium pressure liquid chromatography (ethyl acetate/petroleum ether, 1:2, R_t of **6** = 8 min, R_t of **7** = 9.5 min). Fractions containing single isomers **6** and **7** were evaporated *in vacuo* to give isomerically and analitycally pure compounds **6** and **7**.

The following compounds were prepared in this manner:

Methyl (4*S*,5*S*,8*S*)-4-Cyano-6-oxo-7-oxa-1,2-diazaspiro[4.4]-non-1-ene-8-carboxylate (**6**).

This compound was prepared from **3** and diazomethane (**4**) followed by chromatographic purification and separation. Yield: 0.096 g (43%), mp 115–116° (from ethyl acetate/petroleum ether, 1:2), colorless crystals. $[\alpha]_D^{21}$ = +325° (c = 0.52, dichloro-

methane). Ir (cm^{-1}): 2255 (C≡N), 1785, 1755 (C=O). ^1H nmr (deuteriochloroform): δ 2.90 (1H, dd, J = 6.4, 14.3 Hz, 9–Ha); 3.34 (1H, dd, J = 7.9, 14.3 Hz, 9–Hb); 3.50 (1H, dd, J = 4.5, 9.0 Hz, 4–H); 3.91 (3H, s, OMe); 5.07 (1H, dd, J = 9.0, 18.1 Hz, 3–Ha); 5.22 (1H, dd, J = 4.5, 18.1 Hz, 3–Hb); 5.46 (1H, dd, J = 6.4, 7.9 Hz, 8–H). ^{13}C nmr (deuteriochloroform): δ 29.5, 34.6, 53.8, 74.9, 82.9, 96.5, 116.8, 169.1, 170.0.

Anal. Calcd. for $C_9H_9N_3O_4$ (223.19): C, 48.43; H, 4.06; N, 18.83. Found: C, 48.51; H, 4.01; N, 18.63.

Methyl (4*R*,5*R*,8*S*)-4-Cyano-6-oxo-7-oxa-1,2-diazaspiro[4.4]non-1-ene-8-carboxylate (**7**).

This compound was prepared from **3** and diazomethane (**4**) followed by chromatographic purification and separation. Yield: 0.054 g (24%), mp 120–125° (from ethyl acetate/petroleum ether, 1:2), colorless crystals. $[\alpha]_D^{21}$ = –116° (c = 0.3, dichloromethane). Ir (cm^{-1}): 2254 (C≡N), 1795, 1744 (C=O). ^1H nmr (deuteriochloroform): δ 3.08 (1H, dd, J = 3.0, 14.3 Hz, 9–Ha); 3.18 (1H, dd, J = 9.0, 14.3 Hz, 9–Hb); 3.45 (1H, dd, J = 6.8, 7.9 Hz, 4–H); 3.91 (3H, s, OMe); 5.08–5.15 (2H, m, 3–CH_2); 5.31 (1H, dd, J = 3.0, 9.0 Hz, 8–H). ^{13}C nmr (deuteriochloroform): δ 29.0, 34.4, 53.8, 74.9, 82.6, 96.0, 116.5, 169.0, 170.3.

Anal. Calcd. for $C_9H_9N_3O_4$ (223.19): C, 48.43; H, 4.06; N, 18.83. Found: C, 48.56; H, 4.01; N, 18.53.

General Procedure for the Preparation of Methyl (4*R*,5*S*,8*S*)-3-Aryl-4-cyano-6-oxo-1,7-dioxa-2-azaspiro[4.4]non-2-ene-8-carboxylates (**8a–c**).

A mixture of **3** (0.181 g, 1 mmol), nitrile oxide **5a–c** (1 mmol), and chloroform (10 ml) was refluxed for 2 h. Volatile components were evaporated *in vacuo* and the residue was purified by column chromatography (ethyl acetate/petroleum ether, 1:2). Fractions containing the product were combined and volatile components were evaporated *in vacuo* to give a mixture of isomers **8** and **9** which was purified by medium pressure liquid chromatography. Fractions containing the major (4*R*,5*S*,8*S*)-isomer **8** were evaporated *in vacuo* to give isomerically and analytically pure compound **8** [24].

The following compounds were prepared in this manner:

Methyl (4*R*,5*S*,8*S*)-4-Cyano-6-oxo-3-(2,4,6-trimethylphenyl)-1,7-dioxa-2-azaspiro[4.4]non-2-ene-8-carboxylate (**8a**).

This compound was prepared from **3** and 2,4,6-trimethylbenzonitrile oxide (**5a**), medium pressure liquid chromatography (ethyl acetate/petroleum ether, 1:2, R_t of **8a** = 5 min, R_t of **9a** = 7 min). Yield: 0.094 g (27%), mp 150–152° (from chloroform/*n*-hexane), colorless crystals. Ir (cm^{-1}): 2248 (C≡N), 1796, 1743 (C=O). ^1H nmr (deuteriochloroform): δ 2.32 and 2.34 (9H, 2s, 1:2, 3*Me*–C_6H_2); 2.92 (1H, dd, J = 6.0, 14.7 Hz, 9–Ha); 3.16 (1H, dd, J = 7.5, 14.7 Hz, 9–Hb); 3.88 (3H, s, OMe); 4.85 (1H, s, 4–H); 5.18 (1H, dd, J = 6.0, 7.5 Hz, 8–H); 6.96 (2H, s, C_6H_2). ^{13}C nmr (dimethyl sulfoxide–d_6): δ 20.1, 21.6, 34.3, 48.2, 53.6, 74.7, 87.3, 114.3, 122.7, 129.5, 138.3, 140.9, 153.2, 169.2, 171.8.

Anal. Calcd. for $C_{18}H_{18}N_2O_5$ (342.35): C, 63.15; H, 5.30; N, 8.18. Found: C, 63.16; H, 5.22; N, 7.89.

Minor (4*S*,5*R*,8*S*)-Isomer (**9a**). ^1H nmr (deuteriochloroform): δ 2.32 and 2.33 (9H, 2s, 1:2, 3*Me*–C_6H_2); 3.07 (1H, dd, J = 3.0, 14.7 Hz, 9–Ha); 3.14 (1H, dd, J = 8.3, 14.7 Hz, 9–Hb); 3.92 (3H, s, OMe); 4.91 (1H, s, 4–H); 5.17 (1H, dd, J = 3.0, 8.3 Hz, 8–H); 6.96 (2H, s, C_6H_2).

Methyl (4*R*,5*S*,8*S*)-4-Cyano-6-oxo-3-(2,4,6-trimethoxyphenyl)-1,7-dioxa-2-azaspiro[4.4]non-2-ene-8-carboxylate (**8b**).

This compound was prepared from **3** and 2,4,6-trimethoxybenzonitrile oxide (**5b**), medium pressure liquid chromatography (ethyl acetate/petroleum ether, 1:2, R_t of **8b** = 18.5 min, R_t of **9b** = 22 min). Yield: 0.097 g (25%), mp 204–207° (from chloroform/*n*-hexane), colorless crystals. Ir (cm^{-1}): 2255 (C≡N), 1798, 1757 (C=O). ^1H nmr (deuteriochloroform): δ 2.79 (1H, dd, J = 7.2, 14.7 Hz, 9–Ha); 3.08 (1H, dd, J = 7.2, 14.3 Hz, 9–Hb); 3.86 and 3.87 (12H, 2s, 3:1, 4OMe); 5.16 (1H, deg dd, J = 7.2 Hz, 8–H); 5.34 (1H, s, 4–H); 6.18 (2H, s, C_6H_2). ^{13}C nmr (dimethyl sulfoxide–d_6): δ 34.7, 47.9, 53.6, 56.5, 57.1, 74.4, 86.2, 92.3, 96.2, 114.8, 148.3, 160.7, 164.4, 169.4, 171.7.

Anal. Calcd. for $C_{18}H_{18}N_2O_8$ (390.34): C, 55.39; H, 4.65; N, 7.18. Found: C, 55.47; H, 4.56; N, 6.85.

Minor (4*S*,5*R*,8*S*)-Isomer (**9b**). ^1H nmr (deuteriochloroform): δ 2.96 (1H, dd, J = 3.4, 14.7 Hz, 9–Ha); 3.05 (1H, dd, J = 8.7, 14.7 Hz, 9–Hb); 3.86 and 3.89 (12H, 2s, 3:1, 4OMe); 5.12 (1H, dd, J = 3.4, 8.7 Hz, 8–H); 5.37 (1H, s, 4–H); 6.18 (2H, s, C_6H_2).

Methyl (4*R*,5*S*,8*S*)-4-Cyano-3-(2,6-dichlorophenyl)-6-oxo-1,7-dioxa-2-azaspiro[4.4]non-2-ene-8-carboxylate (**8c**).

This compound was prepared from **3** and 2,6-dichlorobenzonitrile oxide (**5c**), medium pressure liquid chromatography (ethyl acetate/petroleum ether, 1:3, R_t of **8c** = 8 min, R_t of **9c** = 11 min). Yield: 0.178 g (48%), mp 169–173° (from chloroform/*n*-hexane), colorless crystals. Ir (cm^{-1}): 2252 (C≡N), 1797, 1742 (C=O). ^1H nmr (deuteriochloroform): δ 2.93 (1H, dd, J = 6.0, 14.7 Hz, 9–Ha); 3.17 (1H, dd, J = 7.5, 14.7 Hz, 9–Hb); 3.89 (3H, s, OMe); 5.20 (1H, dd, J = 6.0, 7.5 Hz, 8–H); 5.24 (1H, s, 4–H); 7.35–7.50 (3H, m, C_6H_3). ^{13}C nmr (deuteriochloroform): δ 36.4, 47.3, 53.9, 73.8, 87.0, 111.8, 124.5, 129.0, 133.3, 136.3, 148.7, 168.9, 170.2.

Anal. Calcd. for $C_{15}H_{10}Cl_2N_2O_5$ (369.16): C, 48.80; H, 2.73; N, 7.59. Found: C, 48.68; H, 2.56; N, 7.37.

Minor (4*S*,5*R*,8*S*)-Isomer (**9c**). ^1H nmr (deuteriochloroform): δ 3.07 (1H, dd, J = 3.0, 14.7 Hz, 9–Ha); 3.16 (1H, dd, J = 8.7, 14.7 Hz, 9–Hb); 3.92 (3H, s, OMe); 5.19 (1H, dd, J = 3.0, 8.7 Hz, 8–H); 5.29 (1H, s, 4–H); 7.40–7.50 (3H, m, C_6H_3).

Methyl 3-Cyanomethyl-2-methoxyfuran-5-carboxylate (**12**).

Triethylamine (0.1 ml, 0.7 mmol) and a solution of diazomethane (**4**) in diethyl ether (~0.5 *M*, 10 ml, ~5 mmoles) were added to a solution of **3** (0.091 g, 0.5 mmol) in dichloromethane (10 ml) and the solution was left at room temperature for 20 h. Volatile components were left to evaporate in a ventilated hood and the residue was purified by column chromatography (diethyl ether). Fractions containing the product were combined, evaporated *in vacuo*, and the solid residue was crystallized from dichloromethane/diethyl ether to give **12**. Yield: 0.054 g (55%), mp 51–54° (from dichloromethane/diethyl ether), colorless crystals. Ir (cm^{-1}): 2240 (C≡N), 1710, 1630 (C=O). ^1H nmr (deuteriochloroform): δ 3.40 (2H, s, CH_2); 3.85 and 4.10 (6H, 2s, 1:1, 2OMe); 7.15 (1H, s, 4–H).

Anal. Calcd. for $C_9H_9NO_4$ (195.17): C, 55.39; H, 4.65; N, 7.18. Found: C, 55.14; H, 4.54; N, 7.01.

X-Ray Crystallographic Study.

Structures of compounds **6**, **7**, **8a**, and **8c** were solved by direct methods using the SIR92 [25] program. In the structures **6**, **8a**, and **8c**, all hydrogen atoms were located by difference Fourier synthesis and included in refinement with positional parameters and fixed

individual isotropic displacement parameters of the bonded atoms. In the structure of **7** the hydrogen atoms were refined with restrained bonds and angles. All four structures were refined by a full-matrix least-squares procedure on *F* with anisotropic displacement parameters of all non-hydrogen atoms. Empirical weighting schemes were applied for the following three structures: compound **6**: $w = w_f{*}w_s$, w_f (F_o<2.1) = (F_o/2.1), w_f (F_o>8.9) = (8.9/F_o), w_f (2.1<F_o<8.9)=1.0, $w_s(\sin\theta/\lambda<0.53) = ((\sin\theta/\lambda)/0.53)^3$, $w_s(\sin\theta/\lambda>0.70) = (0.7/(\sin\theta/\lambda))^4$, $w_s(0.53<\sin\theta/\lambda<0.70)$ = 1.0, compound **8a**: $w = w_f{*}w_s$, $w_f(F_o<3.8) = (F_o/3.8)^{2.0}$, $w_f(F_o>7.5) = (7.5/F_o)^{1.5}$, w_f (3.8<F_o<7.5)=1.0, $w_s(\sin\theta/\lambda<0.52) = ((\sin\theta/\lambda)/0.52)^2$, $w_s(\sin\theta/\lambda>0.54) = (0.54/(\sin\theta/\lambda))^4$, $w_s(0.52<\sin\theta/\lambda<0.54)$ = 1.0, compound **8c**: $w = w_f{*}w_s$, w_f (F_o<3.6) = (F_o/3.5), w_f (F_o>7.9) = (7.9/F_o), w_f (3.6<F_o<7.9)=1.0, $w_s(\sin\theta/\lambda<0.41) = ((\sin\theta/\lambda)/0.41)^2$, $w_s(\sin\theta/\lambda>0.70) = (0.70/(\sin\theta/\lambda))^4$, $w_s(0.41<\sin\theta/\lambda<0.70)$ = 1.0, and Regina [26] weighting scheme was used for the structure of **7** (Table 1). The Xtal3.4 [27] system of crystallographic programs was used for the reduction of data, structure refinement and interpretation. ORTEPII [28] was used to produce molecular graphics. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 171724 - 171727. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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