Isolation of Methyl (*RS*)-1-*tert*-Butoxycarbonyl-3-cyanomethyl-1,2-dihydro-2-oxo-5*H*-pyrrole-5-carboxylate, the Key-Intermediate in Base-Catalyzed Formation of Racemic Products by 1,3-Dipolar Cycloadditions to Methyl (*S*)-1-*tert*-Butoxycarbonyl-3-[(*E*)-cyanomethylidene]-2-pyrrolidinone-5-carboxylate

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Received January 25, 2002

Cycloadditions of various 1,3-dipoles to methyl (*S*)-1-*tert*-butoxycarbonyl-3-[(*E*)-cyanomethylidene]-2-pyrrolidinone-5-carboxylate (**9**) were studied. Reactions of **9** with diazomethane (**10**) and 2,4,6-trimethoxybenzonitrile oxide (**11**), carried out under neutral conditions, gave the corresponding optically active spiro compounds **16–18** with low diastereoselectivity (20–30% diastereomeric excess). On the other hand, reactions of **9** with nitrile oxide **11** and nitrile imines **14**, **15**, carried out in the presence of a base, afforded racemic pyrazolo and isoxazolo fused 2-pyrrolidinones **21–23** in 82–86% diastereomeric excess. Optically active dipolarophile **9** was isomerized in the presence of basic alumina to give methyl (*RS*)-1-*tert*-butoxycarbonyl-3-cyanomethyl-1,2-dihydro-2-oxo-5*H*-pyrrole-5-carboxylate (**19**). Treatment of the racemic dipolarophile **19** with dipoles **11** and **14**, afforded fused 2-pyrrolidinones **23** and **21**. These observations support compound **19** as the key-intermediate in the formation of racemic cycloadducts **21–23**.

J. Heterocyclic Chem., **39**, 957(2002).

There are numerous examples of naturally occurring and synthetic compounds having a 2-pyrrolidinone structural element. One of the most typical and common examples among these compounds is L-pyroglutamic acid (**1**), which has been widely used for synthetic purposes as a chiral building block [1]. Significant examples of such compounds are also (–)-kainic acid (**2**), (+)-lactacystin (**3**), and spiro and fused pyrrolidinone derivatives **4–7**, which have been prepared as peptide mimetics [2–4] (Figure 1).

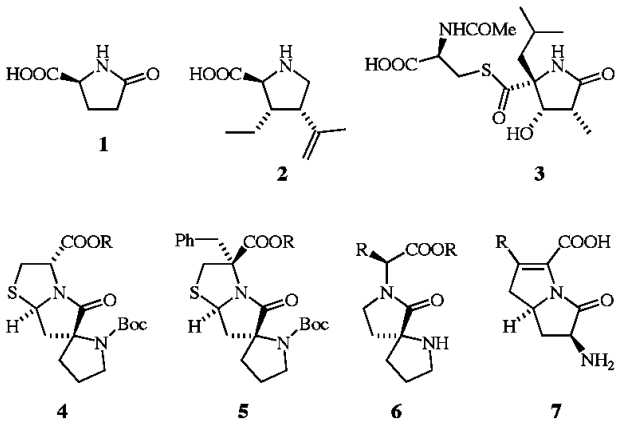


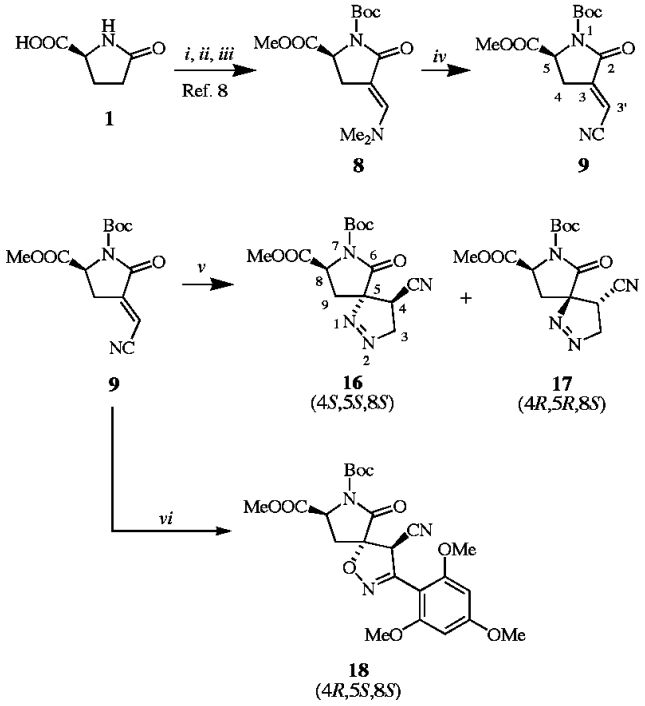
Figure 1

On the other hand, alkyl 2-substituted 3-(dimethylamino)propenoates and alkyl 2-substituted 3-cyanopropenoates are easily available and efficient reagents for the preparation of various heterocyclic systems [5]. Their chiral cyclic analogs, such as 5-substituted (*S*)-1-acyl-3-[(dimethylamino)methylidene]-2-pyrrolidinones and methyl (*S*)-1-benzoyl-3-(cyanomethylidene)-2-pyrrolidinone-5-carboxylate have been employed in preparation of various heterocyclic amino acid derivatives and their analogs [5–8]. Recently, we have reported stereoselective 1,3-dipolar cycloadditions to methyl (*S*)-1-benzoyl-3-[(*E*)-cyanomethylidene]-2-pyrrolidinone-5-carboxylate which, under neutral reaction conditions, afforded optically active spiro cycloadducts, while, in the presence of a base, racemic pyrrolo[3,4–*x*]azoles were formed as cycloadducts. Formation of racemic pyrrolo[3,4–*x*]azoles has been explained *via* initial base induced isomerisation of optically active methyl (*S*)-1-benzoyl-3-[(*E*)-cyanomethylidene]-2-pyrrolidinone-5-carboxylate to give racemic methyl (*RS*)-1-benzoyl-3-cyanomethyl-1,2-dihydro-2-oxo-5*H*-pyrrole-5-carboxylate as the key-intermediate, which then undergoes 1,3-dipolar cycloaddition. Unfortunately, we have been at that time unable to isolate the proposed racemic intermediate [7]. In continuation of our work in this field, we now report the preparation of methyl (*S*)-1-*tert*-butoxycarbonyl-3-[(*E*)-cyanomethylidene]-2-pyrrolidinone-5-carboxylate (**9**), determination of its absolute configuration by X-ray analysis, cycloadditions of various 1,3-dipoles to **9**, as well as the isolation of methyl (*RS*)-1-*tert*-butoxycarbonyl-3-cyanomethyl-1,2-dihydro-2-oxo-5*H*-pyrrole-5-carboxylate (**19**) as the key-intermediate in base catalyzed formation of racemic pyrrolo[3,4–*x*]azole derivatives **21–23**.

Starting compound, methyl (*S*)-1-*tert*-butoxycarbonyl-3-[(*E*)-(dimethylamino)methylidene]-2-pyrrolidinone-5-carboxylate (**8**) was prepared in 3 steps from L-pyroglutamic acid (**1**) according to the procedure described previously [8]. Enaminone **8** was transformed with potassium cyanide in acetic acid into methyl (*S*)-1-*tert*-butoxycarbonyl-3-[(*E*)-

cyanomethylidene]-2-pyrrolidinone-5-carboxylate (**9**) in 63% yield. Compound **9** was then used as chiral dipolarophile in cycloaddition reactions with 1,3-dipoles, such as diazomethane (**10**), 2,4,6-trimethoxybenzonitrile oxide (**11**), *N*-phenylbenzonitrile imine (**14**), and *N*-phenyl-4-chlorobenzonitrile imine (**15**). Nitrile imines **14**, **15** were generated by Huisgen's *in situ* method from the corresponding *N*-phenylbenzohydrazonoyl chlorides **12**, **13** and triethylamine [9]. Generally, all performed 1,3-dipolar cycloadditions of dipoles **10**, **11**, **14**, **15** to the dipolarophile **9** proceeded according to the general reactivity pattern, established previously for the 1-benzoyl analog of **9** [7]. Cycloadditions, carried out under neutral conditions, furnished optically active spiro compounds **16–18**. Thus, reaction of **9** with diazomethane (**10**) afforded methyl (4*S*,5*S*,*8S*)-7-*tert*-butoxycarbonyl-4-cyano-6-oxo-1,2,7-triazaspiro[4.4]non-1-en-8-carboxylate (**16**) and its (4*R*,5*R*,8*S*)-isomer **17** in a ratio of 60:40, respectively. Both isomers, **16** and **17**, were isolated in isomerically pure form upon chromatographic separation. Similarly, cycloaddition of **9** to nitrile oxide **11** furnished methyl (4*R*,5*S*,*8S*)-7-*tert*-butoxycarbonyl-4-cyano-6-oxo-3-(2,4,6-trimethoxyphenyl)-1-oxa-2,7-diazaspiro[4.4]non-2-en-8-carboxylate (**18**) in 30% diastereomeric excess. In this case, however, only the major isomer **18** was isolated in isomerically pure form (Scheme 1).

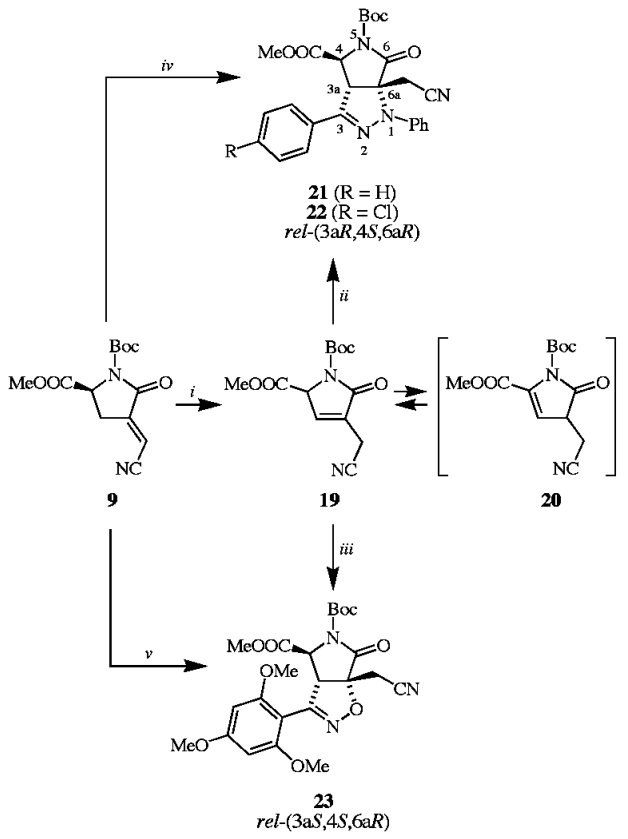
Scheme 1



Reagents and conditions: *i*) $SOCl_2$, MeOH, 0–20°; *ii*) Boc_2O, MeCN, Et_3N, r.t.; *iii*) *t*-BuOCH$(NMe_2)_2$, toluene, 100°; *iv*) KCN, AcOH, 20°; *v*) diazomethane (**10**), Et_2O, CH_2Cl_2, –10°, then chromatographic separation; *vi*) 2,4,6-trimethoxybenzonitrile oxide (**11**), chloroform, reflux, then chromatographic separation.

On the other hand, cycloadditions of nitrile imines **14**, **15** and nitrile oxide **11** to the dipolarophile **9**, carried out in the presence of triethylamine, furnished optically inactive pyrrolo[3,4–*x*]azole derivatives **21–23**. Treatment of **9** with nitrile imines **14**, **15** gave racemic methyl *rel*-(3a*R*,4*S*,6a*R*)-3-aryl-5-*tert*-butoxycarbonyl-6a-cyanomethyl-6-oxo-1-phenyl-3a,6a,4,5-tetrahydro-1*H*,6*H*-pyrrolo[3,4–*c*]pyrazole-4-carboxylates **21**, **22** in 84% and 86% diastereomeric excess, respectively. Analogously, reaction of **9** with nitrile oxide **11** in the presence of triethylamine gave racemic methyl *rel*-(3a*S*,4*S*,6a*R*)-5-*tert*-butoxycarbonyl-6a-cyanomethyl-6-oxo-3-(2,4,6-trimethoxyphenyl)-3a,6a,4,5-tetrahydro-1*H*,6*H*-pyrrolo[3,4–*d*]isoxazole-4-carboxylate (**23**) in 82% diastereomeric excess. Treatment of **9** with basic alumina in dichloromethane at room temperature furnished methyl (*RS*)-1-*tert*-butoxycarbonyl-3-cyanomethyl-1,2-dihydro-2-oxo-5*H*-pyrrole-5-carboxylate (**19**) in 96% yield.

Scheme 2



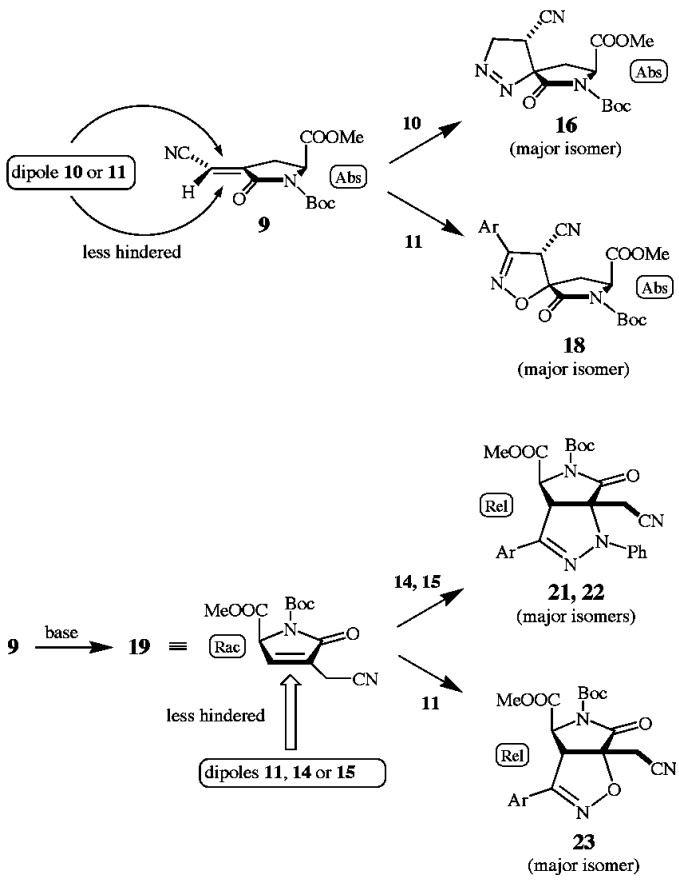
Reagents and conditions: *i*) alumina (*Fluka*, basic, type 5016), CH_2Cl_2, 20°; *ii*) PhC(Cl)NNHPh (**12**), Ag_2O, CH_2Cl_2, 20°, *in situ*: **12** → PhC≡N^+–N^-–Ph (**14**); *iii*) 2,4,6-trimethoxybenzonitrile oxide (**11**), $CHCl_3$, reflux; *iv*) PhC(Cl)NNHPh (**12**) or 4-Cl-C_6H_4-C(Cl)NNHPh (**13**), CH_2Cl_2, Et_3N, reflux, *in situ*: **12** → PhC≡N^+–N^-–Ph (**14**), **13** → 4-Cl-C_6H_4C≡N^+–N^-–Ph (**15**); *v*) 2,4,6-trimethoxybenzonitrile oxide (**11**), $CHCl_3$, Et_3N, reflux.

Cycloadditions of nitrile oxide **11** and nitrile imine **14** to the dipolarophile **19** afforded compounds **23** and **21**, identical with the products obtained from the same dipoles **11**, **14** and the dipolarophile **9** in the presence of triethylamine. Thus, the formation of racemic cycloadducts **21**–**23** can be explained by initial base catalyzed isomerization of optically active dipolarophile **9** into the racemic dipolarophile **19** which then undergoes cycloaddition reaction with dipoles **11**, **14**, **15**. In such a case, racemization of **19** is feasible *via* the intermediate **20**, where the center of chirality at the position 5 is lost (Scheme 2).

Stereoselectivity of cycloadditions to (*S*)-1-*tert*-butoxycarbonyl-3-[(*E*)-cyanomethylidene]-2-pyrrolidinone-5-carboxylate (**9**) is also in agreement with the results reported previously for its 1-benzoyl analog [7]. Thus, cycloadditions of stable dipoles **10**, **11** under neutral conditions gave optically active spiro cycloadducts **16** and **18** with poor stereoselectivity. In these two cases, low stereoselectivity could be attributed to a weak stereoinductive effect of the COOMe group, most probably due to a large distance between the exocyclic C=C bond and the stereodirecting center. In the presence of a base, cycloaddition to **9** proceeds *via* compound **19** as the dipolarophile affording racemic pyrrolo[3,4–*x*]azoles **21**–**23** with much higher stereoselectivity. In these cases, the vicinity of the stereodirecting COOMe group should strongly favour approach of the 1,3-dipole from the sterically less hindered face of the dipolarophile **19** (Scheme 3).

Structures of novel compounds **9**, **16–19**, **21–23** were determined by spectroscopic methods and by elemental analyses for C, H, and N. The structures were in agreement with the structures of closely related compounds, prepared previously [7]. The structure of compound **9** was determined by X–ray structural analysis (Figure 2).

Scheme 3



Compound	Ar	Yield [%]	D.e. [%]
16	-	28	20
18	2,4,6-trimethoxyphenyl	44	30
21	phenyl	39	84
22	4-chlorophenyl	66	86
23	2,4,6-trimethoxyphenyl	60	82

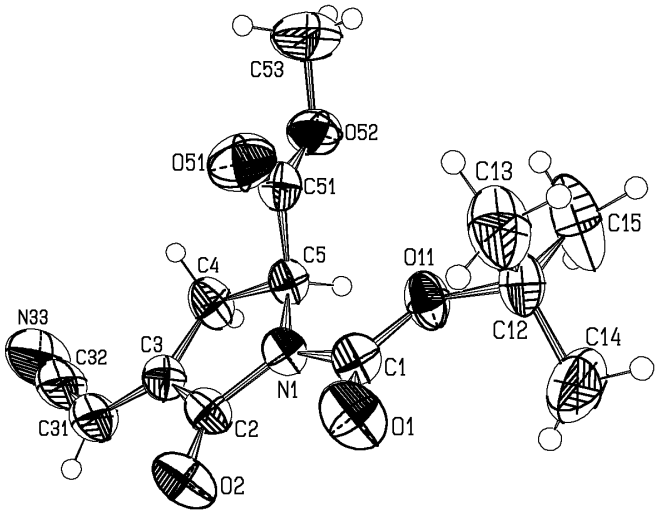


Figure 2. ORTEP view of **9**, showing the molecular structure and labeling of the non-hydrogen atoms. (Ellipsoids at 48% probability level.)

EXPERIMENTAL

Melting points were taken with a Kofler micro hot stage. The ^{1}H nmr (300 MHz) and ^{13}C nmr (75.5 MHz) spectra were obtained with a Bruker Avance DPX 300 (300 MHz) spectrometer with deuteriochloroform and dimethyl sulfoxide–d_6 as solvents and tetramethylsilane as internal standard. Ir spectra were recorded with Perkin-Elmer Spectrum BX FTIR and Perkin-Elmer 1310 spectrophotometers. The microanalyses for C, H, and N were obtained with a Perkin-Elmer CHN Analyser 2400. Tlc: alu foils coated with silica gel 60 F 254, 0.2 mm (Merck). Column chromatography: silica gel (Fluka, silica gel 60, 0.04−0.063 mm). Medium pressure liquid chromatography: Büchi isocratic system with detection [10], silica gel (Merck, silica gel 40, 0.015−0.035 mm); 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.

Table 1

Fractional Coordinates and Equivalent Displacement Parameters (Å^2) for Compound **9**. U_{eq} is Defined as one Third of the Trace of Theorthogonalized U_{ij} Tensor

	x/a	y/b	z/c	U_{eq}
O(1)	0.1684(2)	0.94752	0.6359(3)	0.075(1)
O(11)	0.1002(2)	0.6613(4)	0.7124(2)	0.0543(7)
O(2)	0.3745(2)	0.8217(5)	0.5844(2)	0.069(1)
O(51)	0.3754(3)	0.6194(6)	0.9467(2)	0.081(1)
O(52)	0.3003(2)	0.2802(5)	0.9378(2)	0.0735(9)
N(1)	0.2782(2)	0.6224(4)	0.6878(2)	0.0447(7)
N(33)	0.6897(4)	0.104(1)	0.7042(4)	0.117(2)
C(1)	0.1780(2)	0.7647(5)	0.6753(2)	0.0476(9)
C(12)	-0.0122(2)	0.7745(6)	0.7178(3)	0.057(1)
C(13)	0.0355(4)	0.950(1)	0.8140(5)	0.090(2)
C(14)	-0.0993(4)	0.864(1)	0.5908(5)	0.104(2)
C(15)	-0.0762(6)	0.5909(9)	0.752(1)	0.119(4)
C(2)	0.3673(2)	0.6619(5)	0.6404(2)	0.0460(9)
C(3)	0.4517(2)	0.4649(6)	0.6719(2)	0.0481(8)
C(31)	0.5481(3)	0.4477(7)	0.6390(3)	0.065(1)
C(32)	0.6275(3)	0.2568(8)	0.6736(3)	0.081(2)
C(4)	0.4106(3)	0.3046(6)	0.7406(3)	0.058(1)
C(5)	0.2966(2)	0.4142(5)	0.7546(2)	0.0431(8)
C(51)	0.3282(2)	0.4558(6)	0.8904(2)	0.0515(9)
C(53)	0.3332(7)	0.287(2)	1.0694(4)	0.120(3)

Table 2

Bond Distances (Å) with e.s.d.'s in Parentheses for Compound **9**

O(1)-C(1)	1.196(3)	N(33)-C(32)	1.139(7)
O(11)-C(1)	1.318(4)	C(12)-C(13)	1.488(6)
O(11)-C(12)	1.495(4)	C(12)-C(15)	1.493(9)
O(2)-C(2)	1.202(4)	C(12)-C(14)	1.510(5)
O(51)-C(51)	1.194(4)	C(2)-C(3)	1.490(4)
O(52)-C(51)	1.313(5)	C(3)-C(31)	1.333(5)
O(52)-C(53)	1.440(6)	C(3)-C(4)	1.476(5)
N(1)-C(2)	1.390(4)	C(31)-C(32)	1.428(6)
N(1)-C(1)	1.403(4)	C(4)-C(5)	1.547(5)
N(1)-C(5)	1.464(4)	C(5)-C(51)	1.513(4)

Table 3

Bond angles (°) with e.s.d.'s in Parentheses for Compound **9**

C(1)-O(11)-C(12)	121.4(3)	O(2)-C(2)-C(3)	126.9(3)
C(51)-O(52)-C(53)	116.3(4)	N(1)-C(2)-C(3)	106.0(2)
C(2)-N(1)-C(1)	124.8(3)	C(31)-C(3)-C(4)	128.1(3)
C(2)-N(1)-C(5)	114.2(2)	C(31)-C(3)-C(2)	121.9(3)
C(1)-N(1)-C(5)	121.0(3)	C(4)-C(3)-C(2)	110.0(3)
O(1)-C(1)-O(11)	128.0(3)	C(3)-C(31)-C(32)	119.6(4)
O(1)-C(1)-N(1)	123.4(3)	N(33)-C(32)-C(31)	177.8(5)
O(11)-C(1)-N(1)	108.6(3)	C(3)-C(4)-C(5)	105.2(3)
C(13)-C(12)-C(15)	113.1(5)	N(1)-C(5)-C(51)	110.2(2)
C(13)-C(12)-O(11)	108.9(3)	N(1)-C(5)-C(4)	104.4(2)
C(13)-C(12)-C(14)	111.9(4)	C(51)-C(5)-C(4)	111.1(2)
C(15)-C(12)-O(11)	101.9(4)	O(51)-C(51)-O(52)	125.5(3)
C(15)-C(12)-C(14)	110.5(4)	O(51)-C(51)-C(5)	125.3(3)
O(11)-C(12)-C(14)	110.0(3)	O(52)-C(51)-C(5)	109.2(3)
O(2)-C(2)-N(1)	127.1(3)		

Table 4

Crystal Data, Data Collection, and Refinement data for Compound **9**

Crystal data	
$C_{13}H_{16}N_2O_5$	D_X = 1.234 Mg m^{-3}
M_r = 280.28	Mo $K\alpha$ radiation
Monoclinic, $P2_1$	Cell parameters from 100
a = 11.545(1) Å	reflections
b = 6.1003(8) Å	θ = 9.39-16.35°
c = 11.867(2) Å	μ = 0. 8951 mm^{-1}
β = 115.46(1)°	T = 293(1) K
V = 754.6(2) Å^3	Prism, yellow-brown
Z = 2	0.34 x 0.45 x 0.47 mm
Data collection	
Enraf Nonius CAD-4 diffractometer	θ_{max} = 28°
ω-2θ scans	h = -15 → 15
No absorbtion correction	k = -8 → 8
7290 measured reflections	l = -15 → 15
1978 independent reflections	3 standard reflections
1488 reflections with I>2.5σ(I)	frequency: 333 min
R_{int} = 0.0242	intensity decay: none
Refinement	
Refinement on F	H-atoms parameters refined
R_{obs} = 0.034	w = calculated
wR_{obs} = 0.045	$(\Delta/\sigma)_{max}$ = 0.031
S_{obs} = 0.957	$(\Delta/\sigma)_{ave}$ = 0.0019
1449 reflections	$\Delta\rho_{max}$ = 0.145
246 parameters	$\Delta\rho_{min}$ = -0.155

The range of refined C - H distances was 0.82(9) - 1.19(9) Å.

All starting materials were commercially available (in most cases from Fluka) and purified following the standard techniques. The following compounds were prepared according to the procedures described in the literature: methyl (*S*)-1-*tert*-butoxycarbonyl-3-[(*E*)-(dimethylamino)methylidene]-2-pyrrolidinone-5-carboxylate (**8**) [8], diazomethane (**10**) [11], 2,4,6-trimethoxybenzonitrile oxide (**11**) [12], *N*-phenylbenzohydrazonoyl chloride (**12**), and *N*-phenyl-4-chlorobenzohydrazonoyl chloride (**13**) [9,13].

The diastereomeric excess of compounds **16**, **18**, **21–23** were determined in the following manner: after completion of the reaction, the volatile components were evaporated and the ^{1}H nmr spectra of the residues were recorded. In the case of products **18**/minor isomer, **21**/minor isomer (**21'**) – **23**/minor isomer (**23'**), the major isomers **18**, **21–23** were isolated in analytically pure form, while the corresponding minor isomers **18'**, **21'–23'** were not isolated and were characterized by ^{1}H nmr.

Methyl (*S*)-1-*tert*-Butoxycarbonyl-5-[(*E*)-cyanomethylidene]-2-pyrrolidinone-5-carboxylate (**9**).

Potassium cyanide (0.715 g, 11 mmoles) was dissolved in a solution of **8** (2.980 g, 10 mmoles) in acetic acid (100%, 20 ml) and the solution was left at room temperature for 2 days. The solution was concentrated to one half of the initial volume (~10 ml) by careful evaporation *in vacuo* (T<40°). Water (50 ml) was added to the residue and the product was extracted with diethyl ether (2 x 50 ml). Organic phases were combined and volatile components were evaporated *in vacuo* at 20°. Water (10 ml) and methanol (2 ml) were added to the residue, and the mixture was left at 0–5° for 12 hours. The precipitate was collected by filtration and crystallized from methanol/water (1:2) to give **9**. Yield: 1.760 g (63%), colorless crystals; mp 89–91° (from methanol/water), colorless crystals. Ir (cm^{-1}): 2224 (C≡N), 1779, 1748 (C=O). $[\alpha]_D^{23}$ = +53.7° (*c* = 0.9, dichloromethane). ^{1}H nmr (deuteriochloroform): δ 1.44 (9H, s, *t*-Bu); 3.03 (1H, dt, J = 2.8, 19.6 Hz, 4–Ha); 3.31 (1H, ddd, J = 3.4, 9.8, 19.6 Hz, 4–Hb); 3.83

(3H, s, MeO), 4.76 (1H, dd, J = 2.8, 9.6 Hz, 5–H); 6.35 (1H, t, J = 3.2 Hz, 3'–H). ^{13}C nmr (deuteriochloroform): δ 28.2, 28.3, 53.5, 55.9, 85.5, 103.5, 115.3, 149.3, 151.1, 162.8, 170.8.

Anal. Calcd. for $C_{13}H_{16}N_2O_5$ (280.28): C, 55.71; H, 5.75; N, 9.99. Found: C, 55.46; H, 5.79; N, 9.90.

Methyl (4*S*,5*S*,8*S*)-7-*tert*-Butoxycarbonyl-4-cyano-6-oxo-1,2,7-triazaspiro-[4.4]non-1-en-8-carboxylate (**16**) and Its (4*R*,5*R*,8*S*)-Isomer (**17**).

A cold solution (0°) of diazomethane (**10**) in diethyl ether (~0.42 *M*, 10 ml, 4.2 mmoles) was added to a cold solution (0°) of **9** (0.280 g, 1 mmole) in dichloromethane (5 ml) and the mixture was left at –10 °C for 12 hours. Volatile components were left to evaporate in a well ventilated hood at room temperature and the residue was purified by column chromatography (ethyl acetate/petroleum ether, 1:2). Fractions containing the product were combined and evaporated *in vacuo* to give a mixture of **16** and **17**, which were separated by medium pressure liquid chromatography (ethyl acetate/petroleum ether, 1:2, R_t (**16**) = 7 min, R_t (**17**) = 8.5 minutes). Fractions containing single isomers were evaporated *in vacuo* to give isomerically and analytically pure compounds **16** and **17**.

Methyl (4*S*,5*S*,8*S*)-7-*tert*-Butoxycarbonyl-4-cyano-6-oxo-1,2,7-triazaspiro-[4.4]non-1-en-8-carboxylate (**16**).

This compound was prepared from **9** and diazomethane (**10**) followed by chromatographic separation. Yield: 0.090 g (28%), colorless crystals; mp 125–127°. Ir (cm^{-1}): 2247 (C≡N), 1801, 1760 (C=O). $[\alpha]_D^{22}$ = +463° (*c* = 0.5, dichloromethane). ^{1}H nmr (deuteriochloroform): δ 1.52 (9H, s, *t*-Bu); 2.59 (1H, dd, J = 4.9, 14.3 Hz, 9–Ha); 3.20 (1H, dd, J = 8.7, 14.3 Hz, 9–Hb); 3.46 (1H, dd, J = 4.1, 9.0 Hz, 4–H); 3.87 (3H, s, MeO); 5.00 (1H, dd, J = 9.2, 17.9 Hz, 3–Ha); 5.01 (1H, dd, J = 5.3, 8.7 Hz, 8–H); 5.16 (1H, dd, J = 4.1, 18.1 Hz, 3–Hb). ^{13}C nmr (deuteriochloroform): δ 28.2, 29.7, 30.2, 53.6, 57.2, 82.8, 85.9, 98.8, 117.1, 148.8, 166.8, 171.2.

Anal. Calcd. for $C_{14}H_{18}N_4O_5$ (322.32): C, 52.17; H, 5.63; N, 17.38. Found: C, 52.31; H, 6.00; N, 17.03.

Methyl (4*R*,5*R*,8*S*)-7-*tert*-Butoxycarbonyl-4-cyano-6-oxo-1,2,7-triazaspiro-[4.4]non-1-en-8-carboxylate (**17**).

This compound was prepared from **9** and diazomethane (**10**) followed by chromatographic separation. Yield: 0.081 g (25%), colorless crystals; mp 147–150°. Ir (cm^{-1}): 2248 (C≡N), 1758, 1733 (C=O). $[\alpha]_D^{21}$ = –460° (*c* = 0.5, dichloromethane). ^{1}H nmr (deuteriochloroform): δ 1.55 (9H, s, *t*-Bu); 2.75 (1H, dd, J = 1.5, 14.3 Hz, 9–Ha); 2.94 (1H, dd, J = 9.8, 14.3 Hz, 9–Hb); 3.47 (1H, dt, J = 6.8, 7.2 Hz, 4–H); 3.86 (3H, s, MeO); 5.01 (1H, dd, J = 1.5, 9.8 Hz, 8–H); 5.03–5.07 (2H, m, 3–CH_2). ^{13}C nmr (deuteriochloroform): δ 28.2, 28.7, 31.0, 53.5, 57.3, 82.5, 85.6, 99.8, 117.0, 148.9, 166.8, 170.2.

Anal. Calcd. for $C_{14}H_{18}N_4O_5$ (322.32): C, 52.17; H, 5.63; N, 17.38. Found: C, 52.16; H, 5.66; N, 17.01.

Methyl (4*R*,5*S*,8*S*)-7-*tert*-Butoxycarbonyl-4-cyano-6-oxo-3-(2,4,6-trimethoxyphenyl)-1-oxa-2,7-diazaspiro[4.4]-non-2-en-6-one-8-carboxylate (**18**).

A mixture of **9** (0.280 g, 1 mmole), 2,4,6-trimethoxybenzonitrile oxide (**11**) (0.209 g, 1 mmole), and chloroform (20 ml) was heated under reflux for 2 hours. 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, evaporated *in vacuo*, and the residue was purified by medium pressure liquid chromatography (ethyl acetate/petroleum ether, 1:2, R_t (**18**) = 13.5 min, R_t (**18'**) = 15 minutes). Fractions containing the major isomer **18** were combined and evaporated *in vacuo* to give isomerically and analytically pure **18** [14]. Yield: 0.217 g (44%), colorless crystals; mp 74–77°. Ir (cm^{-1}): 2249 (C≡N), 1800, 1756 (C=O). $[\alpha]_D^{22}$ = +262° (*c* = 0.5, dichloromethane). ^{1}H nmr (deuteriochloroform): δ 1.54 (9H, s, *t*-Bu); 2.56 (1H, dd, J = 5.8, 14.5 Hz, 9–Ha); 2.86 (1H, dd, J = 8.3, 14.7 Hz, 9–Hb); 3.82 (3H, s, MeO); 3.85 (9H, s, 3 MeO); 4.76 (1H, dd, J = 5.7, 8.3 Hz, 8–H); 5.33 (1H, s, 4–H); 6.16 (2H, s, C_6H_2). ^{13}C nmr (deuteriochloroform): δ 28.2, 32.8, 48.1, 53.4, 55.9, 56.1, 56.5, 85.5, 87.8, 91.4, 96.6, 113.8, 147.4, 149.0, 160.7, 164.2, 168.1, 171.0.

Anal. Calcd. for $C_{23}H_{27}N_3O_9$ (489.48): C, 56.44; H, 5.56; N, 8.58. Found: C, 56.15; H, 5.49; N, 8.37.

Minor Isomer (**18'**). ^{1}H nmr (deuteriochloroform): δ 1.55 (9H, s, *t*-Bu); 2.70 (1H, dd, J = 2.3, 14.7 Hz, 9–Ha); 2.80 (1H, dd, J = 9.2, 14.9 Hz, 9–Hb); 3.85 (12H, s, 4 MeO); 4.80 (1H, dd, J = 2.3, 9.0 Hz, 8–H); 5.43 (1H, s, 4–H); 6.17 (2H, s, C_6H_2).

Methyl (*RS*)-1-*tert*-Butoxycarbonyl-3-cyanomethyl-1,2-dihydro-2-oxo-5*H*-pyrrole-5-carboxylate (**19**).

Alumina (0.500 g, Fluka, basic, type 5016) was added to a solution of **9** (0.457 g, 1.63 mmoles) in dichloromethane (10 ml) and the mixture was stirred at room temperature for 12 hours. The reaction mixture was filtered and the filtrate was evaporated *in vacuo* to give **19**. Yield: 0.439 g (96%), colorless crystals; mp 105–107°. $[\alpha]_D^{21}$ = ±0.6° (*c* = 4.39, dichloromethane). Ir (cm^{-1}): 2255 (C≡N), 1779, 1750, 1702 (C=O). ^{1}H nmr (deuteriochloroform): δ 1.52 (9H, s, *t*-Bu); 3.40 (2H, t, J = 2.1 Hz, CH_2CN); 3.83 (3H, s, MeO), 5.18 (1H, dd, J = 2.3, 4.5 Hz, 5–H); 7.15 (1H, dt, J = 1.9, 2.6 Hz, 4–H). ^{13}C nmr (deuteriochloroform): δ 15.6, 28.2, 53.6, 63.1, 84.7, 115.8, 132.0, 138.7, 148.5, 166.3, 166.8.

Anal. Calcd. for $C_{13}H_{16}N_2O_5$ (280.28): C, 55.71; H, 5.75; N, 9.99. Found: C, 55.48; H, 5.82; N, 10.00.

Methyl *rel*-(3a*R*,4*S*,6a*R*)-5-*tert*-Butoxycarbonyl-6a-cyanomethyl-1,3-di-phenyl-6-oxo-3a,6a;4,5-tetrahydro-1*H*,6*H*-pyrrolo[3,4–*c*]pyrazole-4-carboxylate (**21**).

Procedure A.

A mixture of **9** (0.280 g, 1 mmole), *N*-phenylbenzohydrazonoyl chloride (**12**) (0.231g, 1 mmole), triethylamine (0.2 ml, 2 mmoles), and dichloromethane (5 ml) was heated under reflux for 30 minutes. Volatile components were evaporated *in vacuo*, and ethanol (10 ml) was added to the residue. The mixture was cooled to –15° and the precipitate was collected by filtration to give **21**.

Procedure B.

Silver oxide (0.116 g, 0.5 mmole) was added to a solution of **19** (0.123 g, 0.44 mmole) and hydrazonoyl chloride **12** (0.100 g, 0.44 mmole) in dichloromethane (5 ml). The mixture was stirred at room temperature for 72 hours, filtered, and the filtrate was evaporated *in vacuo*. The residue was triturated with ethanol (2.5 ml), cooled to –15°, and the precipitate was collected by filtration to give **21**. Yield: 0.184 g (39%) (Procedure A), 0.022 g (22%) (Procedure B); colorless crystals; mp 164–166° (from ethanol). Ir (cm^{-1}): 2254 (C≡N), 1764, 1732, 1723 (C=O). ^{1}H nmr (dimethyl sulfoxide–d_6): δ 1.38 (9H, s, *t*-Bu); 3.11 (1H, d, J = 17.3 Hz, 1H

of CH_2CN); 3.53 (1H, d, J = 17.3 Hz, 1H of CH_2CN); 3.84 (3H, s, MeO); 4.69 (1H, d, J = 3.4 Hz, 3a–H); 4.88 (1H, d, J = 3.0 Hz, 4–H); 7.05 (1H, t, J = 7.3 Hz, 1H of Ph); 7.36 (2H, t, J = 7.9 Hz, 2H of Ph); 7.48–7.57 (5H, m, 5H of Ph); 7.86 (2H, d, J = 7.9 Hz, 2H of Ph). ^{13}C nmr (dimethyl sulfoxide–d_6): δ 21.8, 28.1, 51.4, 53.9, 61.3, 74.9, 85.1, 116.7, 118.5, 123.4, 127.3, 129.7, 129.9, 130.5, 130.6, 142.8, 148.5, 148.6, 168.5, 171.0.

Anal. Calcd. for $C_{26}H_{26}N_4O_5$ (474.51): C, 65.81; H, 5.52; N, 11.81. Found: C, 65.81; H, 5.81; N, 11.71.

Minor isomer (**21'**). ^{1}H nmr (dimethyl sulfoxide–d_6): δ 4.93 (1H, d, J = 10.2 Hz, 3a–H); 5.18 (1H, d, J = 10.2 Hz, 4–H).

Methyl *rel*-(3a*R*,4*S*,6a*R*)-5-*tert*-Butoxycarbonyl-3-(4-chlorophenyl)-6a-cyanomethyl-6-oxo-1-phenyl-3a,6a;4,5-tetrahydro-1*H*,6*H*-pyrrolo[3,4–*c*]-pyrazole-4-carboxylate (**22**).

A mixture of **9** (0.280 g, 1 mmole), *N*-phenyl-4-chlorobenzohydrazonoyl chloride (**13**) (1 mmole), triethylamine (0.2 ml, 2 mmoles), and dichloromethane (5 ml) was heated under reflux for 30 minutes. Volatile components were evaporated *in vacuo*, and ethanol (10 ml) was added to the residue. The mixture was cooled to –15° and the precipitate was collected by filtration to give **22**. Yield: 0.338 g (66%), colorless crystals; mp 175–177° (from ethanol). Ir (cm^{-1}): 2252 (C≡N), 1797, 1759, 1731 (C=O). ^{1}H nmr (dimethyl sulfoxide–d_6): δ 1.38 (9H, s, *t*-Bu); 3.11 (1H, d, J = 17.3 Hz, 1H of CH_2CN); 3.51 (1H, d, J = 17.3 Hz, 1H of CH_2CN); 3.84 (3H, s, MeO); 4.70 (1H, d, J = 3.4 Hz, 3a–H); 4.88 (1H, d, J = 3.0 Hz, 4–H); 7.01 (1H, t, J = 7.3 Hz, 1H of Ar); 7.36 (2H, t, J = 7.9 Hz, 2H of Ar); 7.53 (2H, d, J = 7.9 Hz, 2H of Ar); 7.61 (2H, d, J = 8.7 Hz, 2H of Ar); 7.86 (2H, d, J = 8.6 Hz, 2H of Ar). ^{13}C nmr (dimethyl sulfoxide–d_6): δ 21.8, 28.1, 51.3, 53.9, 61.2, 75.2, 85.1, 114.5, 118.6, 121.5, 121.8, 123.5, 129.5, 129.6, 129.8, 130.0, 135.0, 142.6, 144.8, 147.6, 168.4, 170.9.

Anal. Calcd. for $C_{26}H_{25}ClN_4O_5$ (508.95): C, 61.36; H, 4.95; N, 11.01. Found: C, 60.97; H, 5.18; N, 11.05.

Minor isomer (**22'**). ^{1}H nmr (dimethyl sulfoxide–d_6): δ 5.08 (1H, d, J = 10.2 Hz, 3a–H); 5.48 (1H, d, J = 10.2 Hz, 4–H).

Methyl *rel*-(3a*S*,4*S*,6a*R*)-5-*tert*-Butoxycarbonyl-6a-cyanomethyl-6-oxo-3a,6a;4,5-tetrahydro-3-(2,4,6-trimethoxyphenyl)-1*H*,6*H*-pyrrolo[3,4–*d*]-isoxazole-4-carboxylate (**23**).

Procedure A.

A mixture of compound **9** (0.280 g, 1 mmole), 2,4,6-trimethoxybenzonitrile oxide (**11**) (0.209 g, 1 mmole), chloroform (5 ml), and triethylamine (0.2 ml, 1.5 mmoles) was heated under reflux for 2 hours. Volatile components were evaporated *in vacuo*, and ethanol (10 ml) was added to the residue. The mixture was cooled to –15°, and the precipitate was collected by filtration to give **23**.

Procedure B.

A mixture of compound **19** (0.140 g, 0.5 mmole), 2,4,6-trimethoxybenzonitrile oxide (**11**) (0.209 g, 1 mmole), and chloroform (5 ml) was heated under reflux for 3 hours. Volatile components were evaporated *in vacuo*, and ethanol (5 ml) was added to the residue. The mixture was cooled to –15° and the precipitate was collected by filtration to give **23**. Yield: 0.292 g (60%) (Procedure A), 0.177 g (72%) (Procedure B), colorless crystals; mp 158–160° (from ethanol). Ir (cm^{-1}): 2259 (C≡N), 1792, 1765, 1740 (C=O). ^{1}H nmr (dimethyl sulfoxide–d_6): δ 1.42 (9H, s, *t*-Bu); 3.20 (1H, d, J = 17.7 Hz, 1H of CH_2CN); 3.39 (1H, d, J = 17.3 Hz, 1H of CH_2CN); 3.71 (6H, s, 2MeO); 3.75 (3H, s, MeO); 3.84 (3H, s, MeO); 4.35 (1H, d, J = 1.1 Hz, 3a–H); 4.41 (1H, d, J = 1.0 Hz, 4–H); 6.37 (2H, s, C_6H_2). ^{13}C nmr (dimethyl sulfoxide–d_6): δ 22.4, 28.1, 53.8, 54.2, 56.5, 56.9, 59.0, 85.5, 86.4, 92.2, 96.3, 116.4, 148.8, 154.3, 160.2, 164.1, 168.5, 170.2.

Anal. Calcd. for $C_{23}H_{27}N_3O_9$ (489.48): C, 56.44; H, 5.56; N, 8.58. Found: C, 56.14; H, 5.66; N, 8.21.

Minor isomer (**23'**). ^{1}H nmr (dimethyl sulfoxide–d_6): δ 4.98 (1H, d, J = 8.7 Hz, 3a–H); 5.54 (1H, d, J = 8.3 Hz, 4–H).

X-Ray Crystallographic Analysis for Compound **9**.

Structure was solved by direct methods using the SIR92 [15] program. Hydrogen atoms were mainly located by an intermediate difference Fourier synthesis, partially calculated (four of them) and included in refinement with isotropic displacement parameters. Full-matrix least-squares refinement on F of all non-hydrogen atoms with anisotropic displacement parameters and an empirical weighting scheme: $w = 14.68*w_F*w_S$, $w_F(F_O<1.45) = (F_O/1.45)$, $w_F(F_O>4.5) = (4.5/F_O)$, $w_F(1.45<F_O<4.5) = 1.0$, $w_S(\sin\theta/\lambda<0.49) = ((\sin\theta/\lambda)/0.49)^{1.5}$, $w_S(\sin\theta/\lambda>0.63) = (0.63/(\sin\theta/\lambda))^6$, $w_s(0.49<\sin\theta/\lambda<0.63) = 1.0$. Absolute configuration on the stereocenter was confirmed by refining the Flack structure parameter.

The results of the structure analysis are presented in Tables 1–4. The molecular structure is shown in Figure 2. The Xtal 3.4 [16] system of crystallographic programs was used for the correlation and reduction of data, structure refinement and interpretation. ORTEPII [17] was used to produce molecular graphics. Calculations were performed on PC computer with Pentium processor and on VAX 8550 computer at the University Computer Center, Ljubljana.

Acknowledgements.

The financial support from the Ministry of Science and Technology, Slovenia, through grant PS-0502-0103, is gratefully acknowledged. The authors also wish to express their gratitude to the Alexander von Humboldt Foundation, Germany, for the donation of a Büchi medium pressure liquid chromatograph.

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