Stereoselective 1,3-Dipolar Cycloadditions to (*S*)-1-Benzoyl-3-(cyanomethylidene)-5-(methoxycarbonyl)pyrrolidin-2-one

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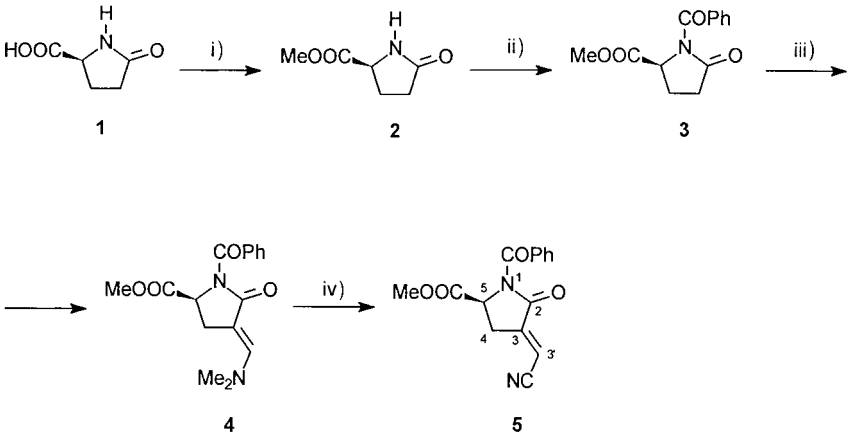
(5*S*)-1-Benzoyl-3-[(*E*)-cyanomethylidene]-5-(methoxycarbonyl)pyrrolidin-2-one (**5**) was prepared in four steps from L-pyroglutamic acid (**1**). 1,3-Dipolar cycloadditions of diazomethane (**6**) and 2,4,6-trimethoxybenzonitrile oxide (**7**) gave substituted 1,2,7-triazaspiro[4.4]non-1-en-6-one **12** and 1-oxa-2,7-diazaspiro[4,4]non-1-en-6-one **13** in 38 and 20% de, respectively. On the other hand, reaction of **5** with *N*-phenylbenzonitrile imines **8** and **9**, generated *in situ* from the corresponding hydrazonoyl chlorides **10** and **11**, respectively, and Et_3N, furnished racemic pyrrolo[3,4-*c*]pyrazoles **14** and **15** in 61 and 56% de, respectively. Cycloaddition of nitrile oxide **7**, when performed in the presence of Et_3N, led to pyrrolo[3,4-*d*]isoxazole **16** in 85% de.

Introduction. – 2-Substituted alkyl 3-(dimethylamino)prop-2-enoates as polyfunctional compounds are very useful reagents for the preparation of a variety of heterocyclic systems including those with α-amino and α-hydroxy acid structural element [1][2]. Substitution of the Me_2N group by a CN group leads to 2-substituted 3-cyanoprop-2-enoates which we also found as versatile reagents for the preparation of heterocyclic systems such as pyrroles, pyridazines, and pyrimidines [3]. 3-Cyanopropenoates can also act as dipolarophiles in 1,3-dipolar cycloaddition reactions [3]. In continuation of our work in this field, we report on the preparation of (5*S*)-1-benzoyl-3-[(*E*)-cyanomethylidene]-5-(methoxycarbonyl)pyrrolidin-2-one (**5**) and stereoselectivity of cycloaddition reactions with 1,3-dipoles **6**–**9**, which resulted in the formation of spiro and fused heterocyclic systems **12**–**16**. To our best knowledge, no 1,3-dipolar cycloadditions to 5-substituted 3-(cyanomethylidene)pyrrolidin-2-ones has been previously reported in the literature. Just recently, regioselective 1,3-dipolar cycloadditions of CH_2N_2 (**6**) and *N*-methyl-α-phenylnitrone to 3-(2,2,2-trifluoroethylidene)-γ-lactams were reported to give 6-oxo-1,2,7-triazaspiro[4.4]non-1-ene and 6-oxo-1-oxa-2,7-diazaspiro[4.4]nonane, respectively [4], and, on the other hand, cycloaddition of 2,4,6-trimethylbenzonitrile oxide to (*S*)-1-(*tert*-butoxycarbonyl)-5-(ethoxycarbonyl)-3-methylidenepyrrolidin-2-one was also reported to give (5*S*,8*S*)-7-(*tert*-butoxycarbonyl)-8-(ethoxycarbonyl)-3-(2,4,6-trimethylphenyl)-6-oxo-1-oxa-2,7-diazaspiro[4.4]non-2-ene in a regiospecific and stereoselective manner [5].

Results and Discussion. – Starting from L-pyroglutamic acid (**1**), (5*S*)-1-benzoyl-3-[(*E*)-(dimethylamino)methylidene]-5-(methoxycarbonyl)pyrrolidin-2-one (**4**) was prepared by modified procedures described in the literature[1]), followed by treatment with

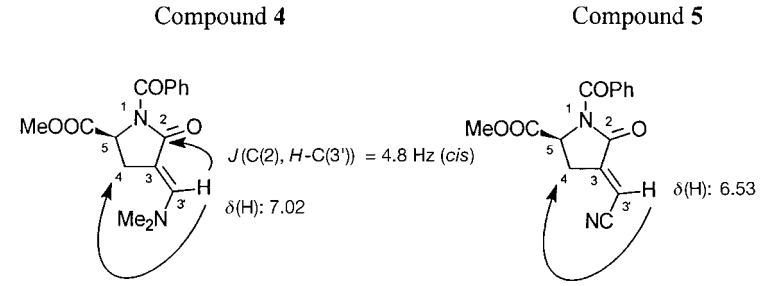
[1]) For the preparation of compound **2**, see [6]; for the preparation of (*S*)-5-(alkoxycarbonyl)-3-[(dimethylamino)methylidene]pyrrolidin-2-ones, see [7].

Scheme 1



i) $SOCl_2$/MeOH, 0° – r.t. ii) MeCN, 4-(dimethylamino)pyridine, Et_3N, PhCOCl. iii) $(Me_2N)_2CH{}^tBu$ toluene, 100°. iv) KCN, AcOH, r.t.

KCN in AcOH to give (5*S*)-1-benzoyl-3-[(*E*)-cyanomethylidene]-5-(methoxycarbonyl)pyrrolidin-2-one (**5**; *Scheme 1*). The configuration of the exocyclic C=C bond in **4** and **5** was determined by NMR. Chemical shifts, coupling constants, and interatomic distances, determined by NOESY experiments, are in agreement with the proposed structure[2]) (*Fig. 1*).



δ(H–C(3′)) [ppm]		δ(H–C(3′)) [ppm]	
Calculated [8]	Found	Calculated [8]	Found
6.75 (*E*)	7.02	6.22 (*E*)	6.53
6.26 (*Z*)		5.46 (*Z*)	

Fig. 1. *NMR Data for the determination of the configuration of the exocyclic C=C bond*

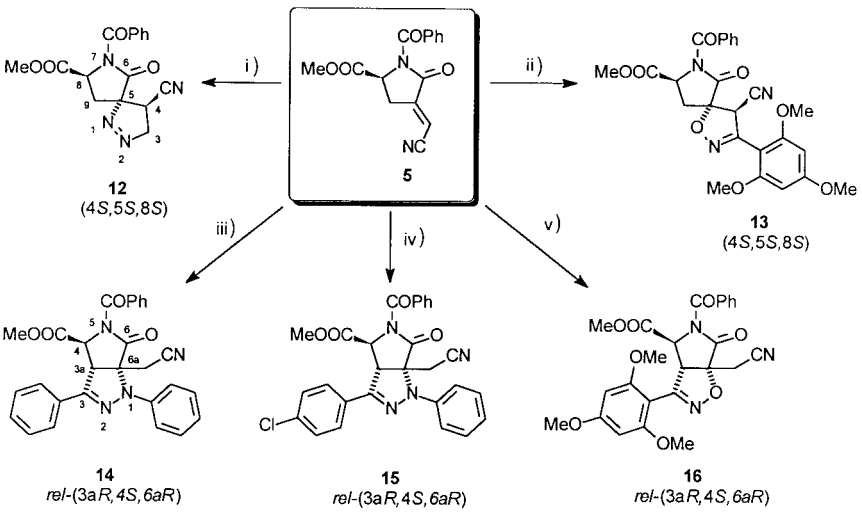
Cycloaddition reactions were performed with the following 1,3-dipoles: CH_2N_2 (**6**) [9], 2,4,6-trimethoxybenzonitrile oxide (**7**) [10], *N*-phenylbenzonitrile imine **8**, and *N*-phenyl-4-chlorobenzonitrile imine **9**. Both compounds, **8** and **9**, were generated by

[2]) Calculated chemical-shift values (δ [ppm]) for olefinic protons (H–C(3′)) in compounds **4** and **5** were obtained by chemical-shift increments [8].

Huisgen's *in situ* method from the corresponding *N*-phenylbenzohydrazonoyl chloride (**10**) and 4-chloro-*N*-phenylbenzohydrazonoyl chloride (**11**), respectively [11–13]. Cycloadditions of 1,3-dipoles **6**–**9** to pyrrolidinone **5** were regiospecific in all cases. Regiochemistry, which was cofirmed by NMR characterization, is also in accordance with regiochemistry of analogous reactions [4][5][14][15].

Cycloaddition of CH_2N_2 (**6**) to pyrrolidinone **5** afforded (4*S*,5*S*,8*S*)-7-benzoyl-4-cyano-8-(methoxycarbonyl)-1,2,7-triazaspiro[4.4]non-1-en-6-one (**12**) together with a diastereoisomer in 38% de. Similarly, treatment with **7** gave (4*S*,5*S*,8*S*)-7-benzoyl-4-cyano-8-(methoxycarbonyl)-1-oxa-2,7-diazaspiro[4.4]-2-en-6-one (**13**) together with a diastereoisomer in 20% de. Isomerically pure compounds **12** and **13** were prepared by crystallization of crude products (*Scheme 2*). The stereoselectivity of these cycloadditions was very poor, probably due to a large distance between the directing stereocenter at C(5) and the reactive site. We also presume that *N*-benzoyl residue, which could be preferably *trans*-oriented with respect to the 5-(methoxycarbonyl) group, contributes to lower the stereoselectivity by directing the 1,3-dipole to approach from the opposite side. However, the degree of stereoselectivity is in accordance with

Scheme 2



i) CH_2N_2 (**6**) Et_2O, $-10°$, 12 h. ii) 2,4,6-Trimethoxybenzonitrile oxide (**7**), $CHCl_3$, reflux, 2 h; iii) *N*-phenylbenzohydrazonoyl chloride (**10**), Et_3N, CH_2Cl_2, reflux, 0.5 h. iv) 4-Chloro-*N*-phenylbenzohydrazonoyl chloride (**11**), Et_3N, CH_2Cl_2, reflux, 0.5 h. v) 2,4,6-Trimethoxybenzonitrile oxide (**7**), Et_3N, CH_2Cl_2, reflux, 0.5 h.

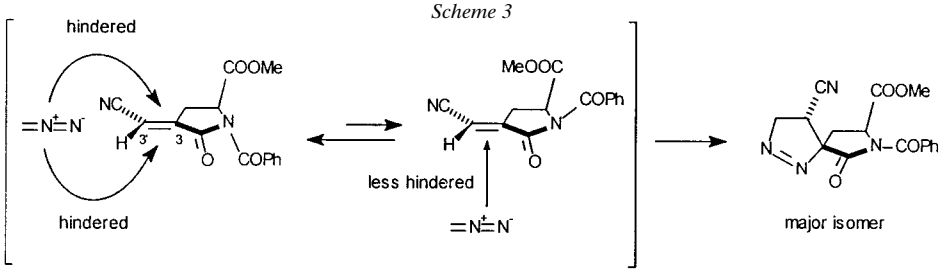
Compound	de [%][a])	Yield[b]) [%]
12	38	42
13	20	44
14	61	36
15	56	47
16	85	58

[a]) Determined by ^{1}H-NMR. [b]) Yield of isolated compound after purification.

that reported for an analogous reaction [5] (*Scheme 3*). The structure of compound **13** was also confirmed by X-ray structural analysis (*Fig. 2* and *Table*).

On the other hand, cycloadditions of nitrile imines **8** and **9** gave racemic *rel*-(3a*R*,4*S*,6a*R*)-3-aryl-5-benzoyl-6a-(cyanomethyl)-4-(methoxycarbonyl)-6-oxo-1-phenyl-3a,6a,4,5-tetrahydro-1*H*,6*H*-pyrrolo[3,4-*c*]pyrazoles **14** and **15** in 61 and 56% de, respectively. Cycloaddition of nitrile oxide **7**, performed in the presence of Et_3N, also gave pyrrolo[3,4-*d*]isoxazole **16** in 85% de (*Scheme 2*). We first thought that Et_3N, used for *in situ* generation of *N*-phenylbenzonitrile imines **8** and **9** from the corresponding *N*-phenylbenzohydrazonoyl chlorides **10** and **11**, respectively, promoted isomerization and racemization of **5** into endocyclic isomer **17**. Consequently, this would explain the formation of pyrrolo[3,4-*c*]pyrazoles **14** and **15**. However, treatment of **5** with CH_2N_2 in the presence of Et_3N, or with Et_3N itself, gave only inseparable mixtures of unidentified products. Although at this moment we do not have a firm proof for the mechanism leading to the formation of racemic fused compounds **14**–**16**, we assume that the tautomeric form **17**, which is in equilibrium with tautomer **18**, might be responsible for racemization and formation of fused compounds **14**–**16**. Preferential approach of 1,3-

Scheme 3



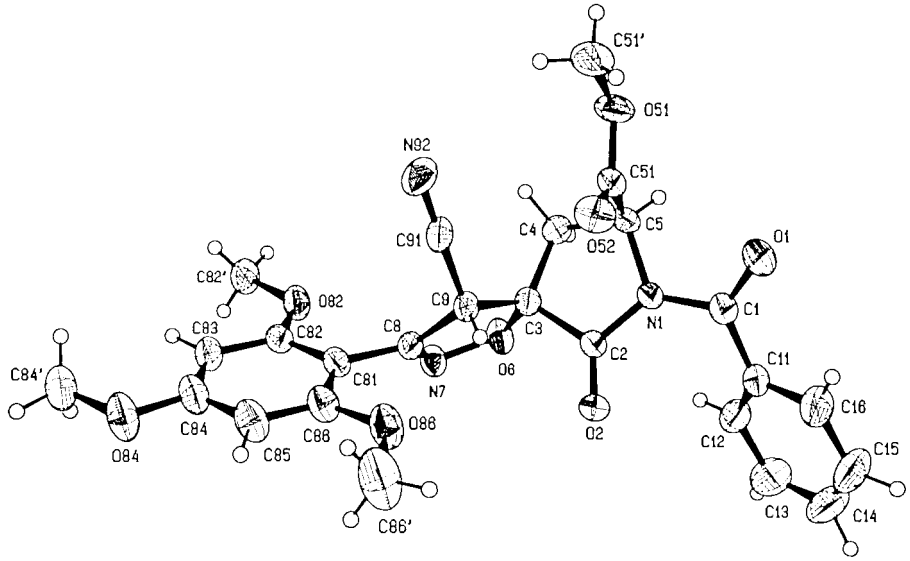


Fig. 2. *ORTEP View of* **13**, *showing the labeling of the non-H-atoms* [16]. Ellipsoids at 40% probability level.

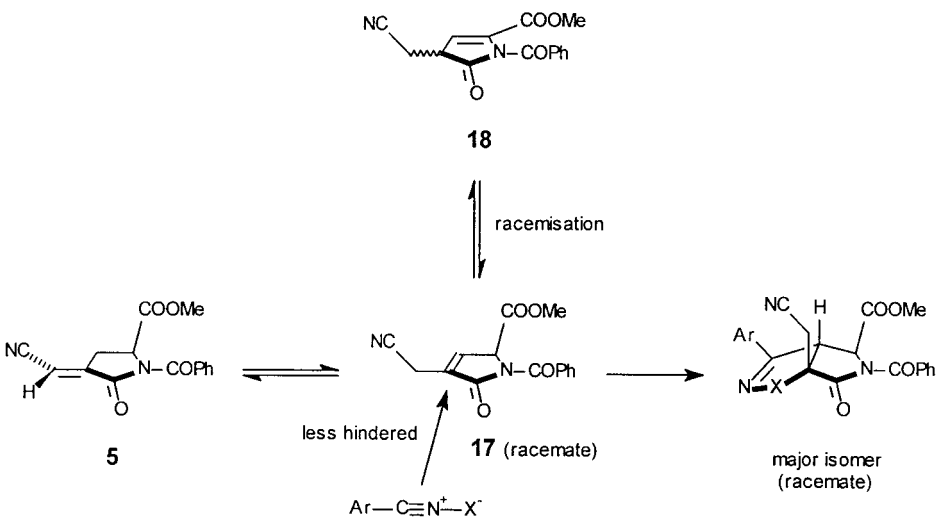
Table. *Crystallographic Data for Compounds* **13** *and* **15**

Compound	**15**	**13**
Crystal Data		
Chemical formula	$C_{28}H_{21}N_4O_4Cl$	$C_{25}H_{23}N_3O_8$
Chemical formula weight	512.95	493.47
Cell setting	Monoclinic	Orthorombic
Space group	*C*12/*c*1	$P2_12_12_1$
a [Å]	22.5566(6)	0.445(1)
b [Å]	7.6837(6)	13.0551(8)
c [Å]	30.0133(2)	18.005(1)
α [°]	90.0000	90.0000
β [°]	103.756(4)	90.0000
γ [°]	90.0000	90.0000
V [Å^3]	5052.65(43)	2455.2(3)
Z	8	4
Density [Mgm^{-3}]	1.349	1.335
Radiation type	MoK_α	MoK_α
Wavelength	0.71069	0.71069
No. of refl. for cell parameters	75	50
θ Range [°]	7.9 – 16.2	10.0 – 16.4
μ [mm^{-1}]	1.8878	0.944
Temp. [K]	293(1)	293(1)
Crystal form	Prism	
Crystal size [mm]	0.65 × 0.49 × 0.21	
Crystal color	Colorless	Colorless
Data Collection		
Diffractometer	*Enraf Nonius CAD-4* diffractometer	
Data collection method	$\omega/2\theta$ scans	
Absorption correction	None	
No. of measured refl.	24409	23740
No. of independent refl.	6530	3328
No. of observed refl.	3312	2464
Criterion of observed refl.	$I > 2.5\sigma(I)$	$I > 2.5\sigma(I)$
R_{int}	0.0216	0.0251
θ_{max} [°]	28	28
Range of *h*, *k*, *l*	$-29 \rightarrow h \rightarrow 29$	$-13 \rightarrow h \rightarrow 13$
	$-10 \rightarrow k \rightarrow 10$	$-17 \rightarrow k \rightarrow 17$
	$-39 \rightarrow l \rightarrow 39$	$-23 \rightarrow l \rightarrow 23$
No. of standard refl.	3	
Frequency of standard refl.	Every 20000 s of scaning time	
Intensity decay [%]	– 8.19	– 0.30

dipoles **7** – **9** from the less hindered side of **17** should give **14** and **16** with *rel*-(3a*R*,4*S*,6a*R*)-configuration. Diastereoselectivity of these reactions was much higher because of the pronounced stereo-inductive effect of the MeOOC group, which is adjacent to the reactive site (*Scheme 4*). The structure of compound **16** was also confirmed by X-ray structural analysis[3]) (*Fig. 3*).

[3]) X-Ray data of structure analyses of the compounds **13** and **16** will be published elsewhere.

Scheme 4



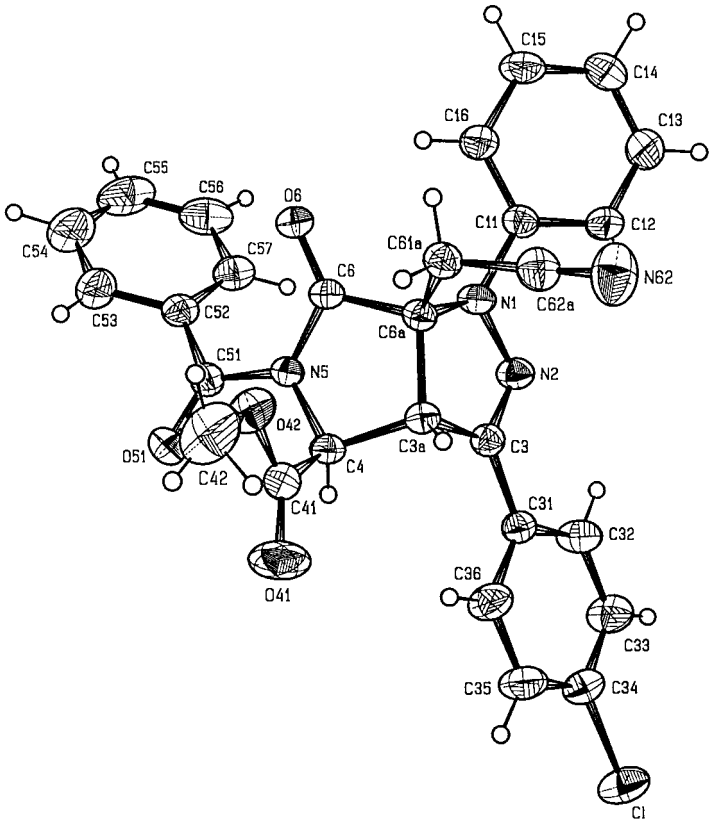


Fig. 3. *ORTEP View of* **15**, *showing the labeling of the non-H-atoms* [16]. Ellipsoids at 35% probability level.

Experimental Part

General. 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: *(*S*)-5-(Methoxycarbonyl)pyrrolidin-2-one* (**2**) [6], CH_2N_2 (**6**) [9], *2,4,6-trimethoxybenzonitrile oxide* (**7**) [10], N-*phenylbenzohydrazonoyl chloride* **10**, and *4-chloro*-N-*phenylbenzohydrazonoyl chloride* **11** [11–13]. Product purifications were performed by flash chromatography (FC) on silica gel (*Fluka*; Kieselgel *60*). TLC: *Merck*, *Alufolien Kieselgel 60 F 254*, 0.2 mm. M.p.: *Kofler* micro hot stage. Optical rotations: *Perkin-Elmer 241 MC* polarimeter. IR: *Perkin-Elmer 1310* spectrophotometer. ^{1}H- and ^{13}C-NMR: *Bruker Avance DPX 300* spectrometer. Elemental analyses: *Perkin-Elmer CHN Analyser 2400*. Crude products **12**–**16** were obtained as mixtures of two isomers: major isomers **12**–**16** and the corresponding minor isomers. Major isomers **12**–**16** were isolated, purified, and fully characterized, while minor isomers were detected and partially characterized by recording the ^{1}H-NMR spectra of crude products. The following workup procedure was applied for ^{1}H-NMR determination of de of compounds **13**–**16**: After completion of reaction, volatile components were evaporated *in vacuo*, and the residue purified by FC. The following eluents were used: $CHCl_3$/MeOH 25:1 (**14**/minor isomer and **15**/minor isomer), Et_2O/petroleum ether 1:1 (**13**/minor isomer and **16**/minor isomer). Fractions containing the product were combined, evaporated *in vacuo*, and ^{1}H-NMR spectra of the residue were recorded.

*(*S*)-*N*-Benzoyl-5-(methoxycarbonyl)pyrrolidin-2-one* (**3**). PhCOCl (7.266 g, 52 mmol) was added to a soln. of *(*S*)-5-(methoxycarbonyl)pyrrolidin-2-one* (**2**; 7.300 g, 50 mmol) in pyridine (75 ml), and the mixture was stirred at r.t. for 2 h. Volatile compounds were evaporated *in vacuo*, hexane (150 ml) was added to the residue, the precipitate collected by filtration, and washed with MeOH (100 ml): 10.374 g (84%) of **3**. M.p. 150–152° (MeOH). $[\alpha]_D^{23} = +30.1$ ($c = 1.1$, CH_2Cl_2). IR (KBr): 1770–1740 (C=O). ^{1}H-NMR (300 MHz, (D_6)DMSO): 2.00–2.04 (*m*, H–C(4)); 2.41–2.47 (*m*, H–C(4)); 2.57–2.62 (*m*, H–C(3)); 3.72 (*s*, MeO); 4.84 (*dd*, $J = 3.9$, 8.7, H–C(5)); 7.42–7.47 (*m*, 2 H of Ph); 7.54–7.61 (*m*, 3 H of Ph). ^{13}C-NMR (75.5 MHz, $CDCl_3$): 22.2; 32.1; 53.1; 59.1; 128.3; 129.5; 132.7; 134.1; 170.8; 172.0; 173.8. Anal. calc. for $C_{13}H_{13}NO_4$ (247.25): C 63.15, H 5.30, N 5.66; found: C 62.96, H 5.20, N 5.58.

*(5*S*)-1-Benzoyl-3-[(*E*)-(dimethylamino)methylidene]-5-(methoxycarbonyl)pyrrolidin-2-one* (**4**). A mixture of **3** (2.473 g, 10 mmol), toluene (20 ml), and *tert*-butyl/bis(dimethylamino)methyl ether (2.610 g, 15 mmol) was heated at 90–100° for 2 h, volatile components were evaporated *in vacuo*, and solid residue was crystallized from AcOEt/hexane 2:1 (15 ml). The precipitate was collected by filtration to give 2.237 g (74%) of **4**. M.p. 133–134° (AcOEt). $[\alpha]_D^{23} = -36.0$ ($c = 1.25$, $CHCl_3$). IR (KBr): 1745, 1720–1700 (C=O). ^{1}H-NMR (300 MHz, (D_6)DMSO): 2.94 (*dd*, $J = 3.1$, 14.8, H–C(4)); 3.02 (*s*, Me_2N); 3.37 (*dd*, $J = 10.7$, 14.6, H–C(4)); 3.69 (*s*, MeO); 4.73 (*dd*, $J = 3.7$, 10.2, H–C(5)); 7.02 (*s*, C*H*NMe_2); 7.35–7.40 (*m*, 2 H of Ph); 7.45–7.51 (*m*, 3 H of Ph). ^{13}C-NMR (75.5 MHz, $CDCl_3$): 27.3; 43.0; 53.3; 56.6; 91.7; 128.3; 129.5; 131.9; 136.1; 148.1; 170.2; 171.7; 172.8. Anal. calc. for $C_{16}H_{18}N_2O_4$ (302.33): C 63.56, H 6.00, N 9.27; found: C 63.34, H 6.35, N 9.13.

*(5*S*)-1-Benzoyl-3-[(*E*)-cyanomethylidene]-5-(methoxycarbonyl)pyrrolidin-2-one* (**5**). A soln. of **4** (2.983 g, 10 mmol) and KCN (0.715 g, 11 mmol) in AcOH (100%, 20 ml) was left at r.t. for 2 d. Then, the soln. was concentrated to one half of the original volume (*ca*. 10 ml) by careful evaporation *in vacuo* ($T < 40°$). H_2O (50 ml) was added to residue and the product extracted with Et_2O (2 × 50 ml). Org. phases were combined and volatile components evaporated *in vacuo* at 20°. H_2O (10 ml) and MeOH (2 ml) were added to the residue, the mixture was cooled (0°), and the precipitate was collected by filtration and crystallized again from MeOH/H_2O 1:2 to give 2.075 g (73%) of **5**. M.p. 119–121° (MeOH/H_2O 1:2). $[\alpha]_D^{23} = +71.5$ ($c = 0.85$, $CHCl_3$). IR (KBr): 2240 (CN), 1750, 1680 (C=O). ^{1}H-NMR (300 MHz, (D_6)DMSO): 3.20 (*dt*, $J = 2.7$, 2.9, 19.2, H–C(4)); 3.49 (*ddd*, $J = 3.4$, 9.4, 19.2, H–C(4)); 3.73 (*s*, MeO); 5.01 (*dd*, $J = 3.4$, 9.4, H–C(5)); 6.53 (*dd*, $J = 2.6$, 3.4, C*H*CN); 7.45–7.51 (*m*, 2 H of Ph); 7.58–7.67 (*m*, 3 H of Ph). ^{13}C-NMR (75.5 MHz, $CDCl_3$): 28.7; 53.7; 55.8; 104.2; 115.2; 128.5; 129.6; 133.1; 133.4; 151.6; 163.4; 170.4; 170.7. Anal. calc. for $C_{15}H_{12}N_2O_4$ (284.27): C 63.38, H 4.26, N 9.85; found: C 63.39, H 4.50, N 9.70.

*(4*S*,5*S*,8*S*)-7-Benzoyl-4-cyano-8-(methoxycarbonyl)-1,2,7-triazaspiro[4.4]non-1-en-6-one* (**12**). A soln. of CH_2N_2 (**6**) in Et_2O (*ca*. 0.67M, 7.5 ml, 5 mmol) was added to a soln. of **5** (0.284 g, 1 mmol) in Et_2O (5 ml). The mixture was left at −10° for 12 h and the precipitate collected by filtration to give a mixture of **12** and its isomer in a ratio of 69:31 (the same ratio of isomers was also obtained after evaporation of the reaction mixture). Yield: 95% (0.30 g). $[\alpha]_D^{23} = +350$ ($c = 0.42$, CH_2Cl_2). Anal. calc. for $C_{16}H_{14}N_4O_4$ (326.31): C 58.89, H 4.32, N 17.17; found: C 58.65, H 4.29, N 17.09.

Crystallization from CH_2Cl_2/Et_2O 3:1 gave 0.136 g (42%) of isomerically pure **12**. M.p. 171–173° (CH_2Cl_2/Et_2O 3:1). $[\alpha]_D^{23} = +433$ ($c = 0.42$, CH_2Cl_2). IR (KBr): 2240 (CN), 1760–1730, 1700–1680 (C=O). ^{1}H-NMR

(300 MHz, (D_6)DMSO): 2.63 (*dd*, *J* = 5.6, 14.0, H–C(9)); 3.24 (*dd*, *J* = 8.2, 13.9, H–C(9)); 3.73 (*dd*, *J* = 4.9, 9.4, H–C(4)); 3.78 (*s*, MeO); 4.97 (*dd*, *J* = 9.4, 18.5, H–C(3)); 5.19 (*dd*, *J* = 5.3, 18.5, H–C(3)); 5.32 (*dd*, *J* = 5.8, 8.5, H–C(8)); 7.49 (*t*, *J* = 7.6, 2 H of Ph); 7.62 (*t*, *J* = 7.5, 2 H of Ph); 7.75 (*d*, *J* = 7.2, 1 H of Ph). ^{13}C-NMR (75.5 MHz, (D_6)DMSO): 28.8; 29.3; 52.8; 56.5; 82.2; 98.2; 117.8; 127.9; 129.3; 132.5; 132.9; 167.9; 169.3; 170.2. Anal. calc. for $C_{16}H_{14}N_4O_4$ (326.31): C 58.89, H 4.32, N 17.17; found: C 58.43, H 4.41, N 17.24. *Minor isomer:* ^{1}H-NMR (300 MHz, (D_6)DMSO): 2.72 (*dd*, *J* = 2.6, 14.3, H–C(9)); 3.12 (*dd*, *J* = 10.2, 14.3, H–C(9)); 3.69 (*dd*, *J* = 4.9, 9.4, H–C(4)); 3.78 (*s*, MeO); 4.94 (*dd*, *J* = 9.4, 18.5, H–C(3)); 5.19 (*dd*, *J* = 4.9, 18.5, H–C(3)); 5.32 (*dd*, *J* = 2.6, 10.2, H–C(8)).

*(4*S*,5*S*,8*S*)-7-Benzoyl-4-cyano-8-(methoxycarbonyl)-3-(2,4,6-trimethoxyphenyl)-1-oxa-2,7-diazaspiro[4.4]-non-2-en-6-one* (**13**). A mixture of **5** (0.284 g, 1 mmol), *2,4,6-trimethoxybenzonitrile oxide* (**7**; 0.209 g, 1 mmol), and $CHCl_3$ (10 ml) was heated under reflux for 2 h, cooled, and volatile compounds were evaporated *in vacuo.* EtOH (10 ml) was added to the residue, the mixture was cooled (– 15°), and the precipitate was collected by filtration to give 0.217 g (44%) of **13**. M.p. 213–215°. $[\alpha]_D^{23} = +400$ (*c* = 0.60, CH_2Cl_2). IR (KBr): 2260 (CN), 1760, 1690 (C=O). ^{1}H-NMR (300 MHz, $CDCl_3$): 2.73 (*dd*, *J* = 14.7, 5.3, H–C(9)); 3.00 (*dd*, *J* = 14.6, 8.3, H–C(9)); 3.82 (*s*, MeO); 3.84 (*s*, MeO); 3.86 (*s*, MeO); 5.01 (*dd*, *J* = 5.5, 8.1, H–C(8)); 5.28 (*s*, H–C(4)); 6.15 (*s*, 2 H of Ar); 7.44–7.49 (*m*, 2 H of Ph); 7.57–7.62 (*m*, 1 H of Ph); 7.72–7.75 (*m*, 1 H of Ph). ^{13}C-NMR (75.5 MHz, $CDCl_3$): 33.1; 48.4; 53.7; 55.86; 55.93; 56.5; 88.2; 91.4; 96.5; 113.8; 128.5; 129.9; 132.8; 133.5; 147.6; 160.7; 164.2; 169.1; 170.0; 171.0. Anal. calc. for $C_{25}H_{23}N_3O_8$ (493.47): C 60.84, H 4.69; N 8.51; found: C 60.62; H 5.04; N 8.42. *Minor isomer:* ^{1}H-NMR (300 MHz, $CDCl_3$): 5.37 (*s*, H–C(4)).

General Procedure for the Preparation of rel-*(3a*R*,4*S*,6a*R*)-3-Aryl-5-benzoyl-6a-(cyanomethyl)-4-(methoxycarbonyl)-6-oxo-1-phenyl-3a,6a,4,5-tetrahydro-1*H*,6*H*-pyrrolo[3,4-*c*]pyrazoles* **14** *and* **15**. A hydrazonoyl chloride **10** or **11** (1.0 mmol) and Et_3N (0.2 ml, 1.5 mmol) were added to a soln. of **5** (0.284 g, 1.0 mmol) in CH_2Cl_2 (5 ml), and the mixture was heated at reflux temp. for 30 min, cooled, and volatile components were evaporated *in vacuo*. EtOH (10 ml) was added to the residue, the mixture was cooled (– 15°), and the precipitate was collected by filtration to give a pyrrolo[3,4-*c*]pyrazole (**14** or **15**).

rel-*(3a*R*,4*S*,6a*R*)-5-Benzoyl-6a-(cyanomethyl)-1,3-diphenyl-4-(methoxycarbonyl)-6-oxo-3a,4,5,6a-tetrahydro-1*H*,6*H-*pyrrolo[3,4-*c*]pyrazole* (**14**). Compound **14** was prepared from **5** (0.284 g, 1.0 mmol), *N*-phenylbenzohydrazonoyl chloride (**10**; 0.231 g, 1.0 mmol), and Et_3N (0.2 ml, 1.5 mmol). Yield: 47% (0.225 g). M.p. 203–205° (EtOH/DMF 20:1). $[\alpha]_D^{23} = -10.3$ (*c* = 0.4, CH_2Cl_2). IR (KBr): 2240 (CN), 1750, 1690 (C=O). ^{1}H-NMR (300 MHz, (D_6)DMSO): 3.12 (*d*, *J* = 17.3, CH_2); 3.59 (*d*, *J* = 17.3, CH_2); 3.86 (*s*, MeO); 4.91 (*d*, *J* = 3.0, H–C(3a)); 5.02 (*d*, *J* = 3.0, H–C(4)); 7.08–7.13 (*m*, 1 H of Ph); 7.33–7.59 (*m*, 12 H of Ph); 7.89–7.92 (*m*, 2 H of Ph). ^{13}C-NMR (75.5 MHz, (D_6)DMSO): 22.5; 52.0; 54.1; 61.0; 75.1; 116.8; 119.3; 123.9; 127.3; 129.0; 129.6; 129.8; 129.9; 130.6; 130.6; 133.2; 133.7; 142.9; 148.9; 169.2; 170.1; 170.9. Anal. calc. for $C_{28}H_2N_4O_4$ (478.51): C 70.28, H 4.63, N 11.71; found: C 70.21, H 4.63, N 11.68. *Minor isomer:* ^{1}H-NMR (300 MHz, (D_6)DMSO): 5.09 (*d*, *J* = 10.2, H–C(3a)); 5.49 (*d*, *J* = 10.2, H–C(4)).

rel-*(3a,4,5-6a*R*)-5-Benzoyl-3-(4-chlorophenyl)-6a-(cyanomethyl)-4-(methoxycarbonyl)-6-oxo-1-phenyl-3a,4,5,6a-tetrahydro-1*H*,6*H-*pyrrolo[3,4-*c*]pyrazole* (**15**). Compound **15** was prepared from **5** (0.284 g, 1.0 mmol), 4-chloro-*N*-phenylbenzohydrazonoyl chloride (**11**; 0.265 g, 1.0 mmol), and Et_3N (0.2 ml, 1.5 mmol). Yield: 36% (0.184 g). M.p. 187–189° (EtOH/DMF 20:1). $[\alpha]_D^{23} = 1.3$ (*c* = 0.30, CH_2Cl_2). IR (KBr): 2260 (CN), 1770–1730, 1690–1670 (C=O). ^{1}H-NMR (300 MHz, (D_6)DMSO): 3.13 (*d*, *J* = 17.7, CH_2); 3.57 (*d*, *J* = 17.3, CH_2); 3.86 (*s*, MeO); 4.92 (*d*, *J* = 3.0, H–C(3a)); 5.03 (*d*, *J* = 3.0, H–C(4)); 7.11 (*t*, *J* = 7.2, 1 H of Ph); 7.33–7.42 (*m*, 6 H of Ph); 7.46 (*m*, 2 H of Ph); 7.54–7.59 (*m*, 1 H of Ph); 7.64 (*d*, *J* = 6.8, 2 H of Ar); 7.90 (*d*, *J* = 6.8, 2 H or Ar). ^{13}C-NMR (75.5 MHz, (D_6)DMSO): 22.4; 51.8; 54.1; 60.9; 75.4; 116.8; 119.3; 124.0; 128.9; 129.0; 129.5; 129.6; 129.8; 129.9; 133.2; 133.7; 135.1; 142.8; 148.0; 169.1; 170.1; 170.8. Anal. calc. for $C_{28}H_{21}N_4O_4Cl$ (512.95): C 65.56, H 4.13, N 10.92; found: C 65.74, H 4.18, N 10.98. *Minor isomer*: ^{1}H-NMR (300 MHz, (D_6)DMSO): 5.08 (*d*, *J* = 10.2, H–C(3a)); 5.48 (*d*, *J* = 10.2, H–C(4)).

rel-*(3a*R*,4*S*,6a*R*)-5-Benzoyl-6a-(cyanomethyl)-4-(methoxycarbonyl)-6-oxo-3-(2,4,6-trimethoxyphenyl)-3a,4,5,6a-tetrahydro-1*H*,6*H-*pyrrolo[3,4-*d*]isoxazole* (**16**). *2,4,6-Trimethoxybenzonitrile oxide* (**7**; 0.209 g, 1.0 mmol), and Et_3N (0.2 ml, 1.5 mmol) were added to a soln. of **5** (0.284 g, 1.0 mmol) in $CHCl_3$ (5 ml), and the mixture was heated at reflux temp. for 2 h, cooled, and volatile components were evaporated *in vacuo*. EtOH (10 ml) was added to the residue, the mixture was cooled (– 15°), and the precipitate was collected by filtration to give 0.286 g (58%) of **16**. M.p. 226–228° (EtOH/DMF 20:1). $[\alpha]_D^{23} = +0.4$ (*c* = 0.98, CH_2Cl_2). ^{1}H-NMR (300 MHz, (D_6)DMSO): 3.26 (*d*, *J* = 17.3, CH_2); 3.42 (*d*, *J* = 17.3, CH_2); 3.71 (*s*, MeO); 3.74 (*s*, MeO); 3.85 (*s*, MeO); 4.46 (*d*, *J* = 0.9, H–C(3a)); 4.65 (*d*, *J* = 1.0, H–C(4)); 6.37 (*s*, 2 H of Ar); 7.53–7.60 (*m*, 4 H of Ar); 7.64–7.72 (*m*, 1 H of Ar). ^{13}C-NMR (75.5 MHz, (D_6)DMSO): 22.1; 54.3; 54.5; 56.5; 57.0; 58.8; 86.9; 92.2; 96.2; 116.5;

129.4; 129.5; 132.9; 134.3; 154.6; 160.2; 169.6; 169.9; 170.2. Anal. calc. for $C_{25}H_{23}N_3O_8$ (493.47): C 60.84, H 4.69, N 8.51; found: C 60.47, H 4.81, N 8.44. *Minor isomer:* ^{1}H-NMR (300 MHz, (D_6)DMSO): 4.75 (*d*, *J* = 4.9, H–C(3a)).

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