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ORIGINAL PAPER

Synthesis and stereochemistry of some novel dihydropyrrolo[3,4-*c*]pyrazoles

Yaşar Dürüst · Muhammet Yıldırım · Chris F. Fronczek · Frank R. Fronczek

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Abstract Eleven novel dihydropyrrolo[3,4-*c*]pyrazole derivatives were obtained by the reaction of chiral (1*R*)-*N*-(1-phenylethyl)maleimide and C,N-aryl-substituted nitrilimines. The reaction afforded the cycloadducts as a regioisomeric mixture which can be separable in some cases. The structure and stereochemistry of cycloadducts were assigned on the basis of infrared (IR), ^{1}H and ^{13}C nuclear magnetic resonance (NMR), mass and X-ray spectra, optical rotation measurements, and CHN analyses.

Keywords Nitrilimine · Chiral maleimide · 1,3-Dipolar cycloaddition · Ylide

Introduction

Nitrilimines, which were discovered by Huisgen and coworkers in 1959, are important precursors of 1,3-dipolar structure which can be used to assemble a wide variety of five-membered nitrogen-containing heterocyclic compounds with 1,3-dipolar cycloaddition reactions to various dipolarophiles leading to five- or six-membered, or larger heterocycles [1–22]. Experimental observations showed that the orientation observed for alkenes substituted with electron-donor, conjugating, and moderate electron-acceptor substituents is the 5-substituted regioisomer [23–26]. Sometimes the cycloadditions of nitrilimines to very electron-deficient alkenes give significant amounts of the 4-substituted 2-pyrazolines [27]. The rationalization of such regiochemical results became evident in terms of the frontier molecular orbital (FMO) theory of Fukui [28–37].

On the other hand, maleimides are an important class of substrates for biological and chemical applications [38–43]. Their reactivity as a dipolarophile in 1,3-dipolar cycloadditions has been utilized in many examples of cycloaddition chemistry [44].

As part of our continued interest in nitrilimine cycloaddition research [45], due to limited numbers of cycloaddition reactions of chiral maleimides with dipolar compounds such as nitrones, nitriloxides, and anthrones reported in the literature [46–54] to the best of our knowledge, we were encouraged to carry out 1,3-dipolar cycloadditions of C,N-substituted nitrilimines to chiral (1*R*)-*N*-(1-phenylethyl)maleimide to assemble pyrrolo[3,4-*c*]pyrazoles bearing chiral centers.

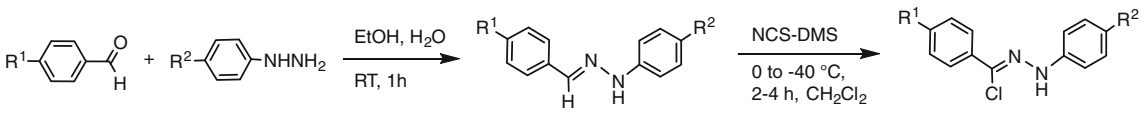
Results and discussion

Hydrazones **3** were prepared from the appropriate *para*-substituted aromatic aldehydes and hydrazines according to literature procedures [53, 54], and hydrazonyl chlorides **4** were obtained from the above hydrazones by using the method reported by Kim and Corey (*N*-chlorosuccinimide-dimethyl sulfide) [53–55] (Scheme 1). Chiral maleimide **6** was prepared by reacting chiral amine **5** with maleic anhydride followed by acetic anhydride (Scheme 2).

Cycloaddition reactions of the nitrilimines which were generated in situ by the effect of triethylamine on hydrazonyl chlorides to chiral maleimide **6** were carried out in dry acetonitrile at room temperature. Thus, 11 novel pyrrolo[3,4-*c*]pyrazoles **7a–8k** were obtained in good yields (Scheme 3, Table 1).

Y. Dürüst (✉) · M. Yıldırım
Department of Chemistry, Abant İzzet Baysal University, 14280 Bolu, Turkey
e-mail: yasardurust@ibu.edu.tr

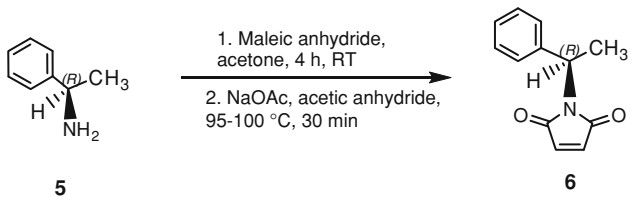
C. F. Fronczek · F. R. Fronczek
Department of Chemistry, Louisiana State University, Baton Rouge, LA 70803-1804, USA



1 2 3a-3k 4a-4k

3,4	R^1	R^2	3,4	R^1	R^2
a	H	H	**g**	OCH_3	H
b	Cl	H	**h**	SCH_3	H
c	Br	H	**i**	$OCOCH_3$	H
d	F	H	**j**	CH_3	CN
e	CN	H	**k**	NO_2	Cl
f	CF_3	H			

Scheme 1



5 6

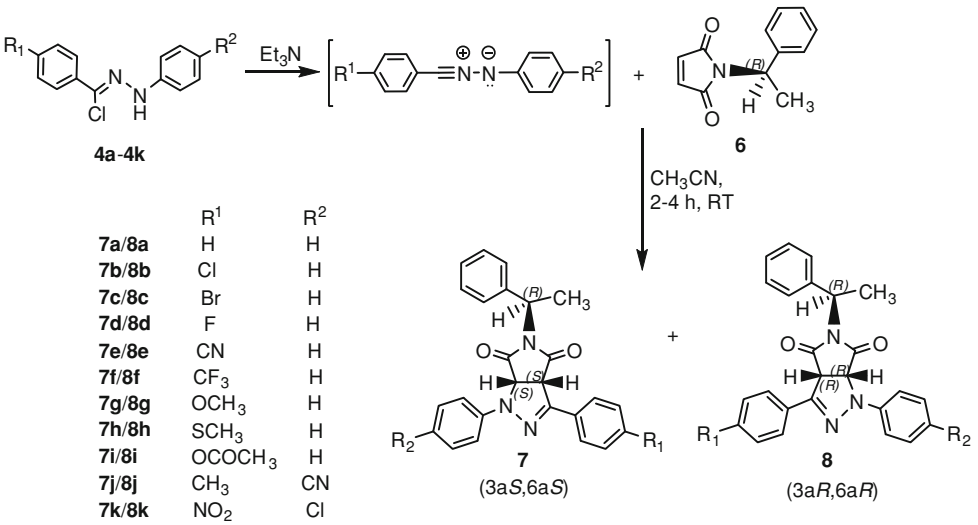
Scheme 2

Structure determination of the new compounds was performed on the basis of IR, ^{1}H NMR, ^{13}C NMR, mass spectrometry (MS), X-ray diffraction spectra, and elemental analyses. All cycloadducts showed strong absorption around 1,705–1,712 cm^{-1} due to two carbonyl groups and absorptions relating to the C=N around 1,600 cm^{-1} in the IR spectra. Crude ^{1}H NMR spectra of the cycloadducts obtained after the usual work-up showed only one single diastereomer in each case, and after purification doublet of doublet patterns related to the bridge protons (3a–H and 6a–H) and a quintet pattern related to the C–H (phenethyl on maleimide nitrogen) were observed. At first sight, when we examined the doublets, it could be clearly seen that 3a–H and 6a–H protons make couplings with the *ortho* hydrogens of the phenyl groups as depicted in the structure of **8f**. Also there is a quintet splitting pattern arising from the couplings of methyl protons and phenyl *ortho* hydrogen with the C–H proton. In the case of dimethyl sulfoxide (DMSO)-d_6 as NMR solvent it appeared as triplet (Figs. 1, 2). Methyl protons of the chiral maleimide portion were also coupled with both C–H and phenyl *ortho* hydrogens, causing a triplet splitting (Fig. 3).

Stereochemistry of the cycloadducts was determined based on the X-ray diffraction data and NMR spectra. Theoretically, the unsymmetrical nitrilimine 1,3-dipole may approach chiral maleimide in two different orientations, leading to the formation of cycloadducts **7** and **8** regioselectively (Scheme 4).

The structure elucidation of the chiral cycloadducts **7/8** was established by means of spectroscopic and physical data including IR, NMR, gas chromatography (GC)–MS, CHN analyses, and most importantly by X-ray diffraction data. After recrystallization of the cycloadducts from appropriate solvents, fine crystals were obtained, which allowed us to determine the stereochemistry of the chiral

Scheme 3



4a-4k 6

	R^1	R^2
7a/8a	H	H
7b/8b	Cl	H
7c/8c	Br	H
7d/8d	F	H
7e/8e	CN	H
7f/8f	CF_3	H
7g/8g	OCH_3	H
7h/8h	SCH_3	H
7i/8i	$OCOCH_3$	H
7j/8j	CH_3	CN
7k/8k	NO_2	Cl

7 (3a*S*,6a*S*) 8 (3a*R*,6a*R*)

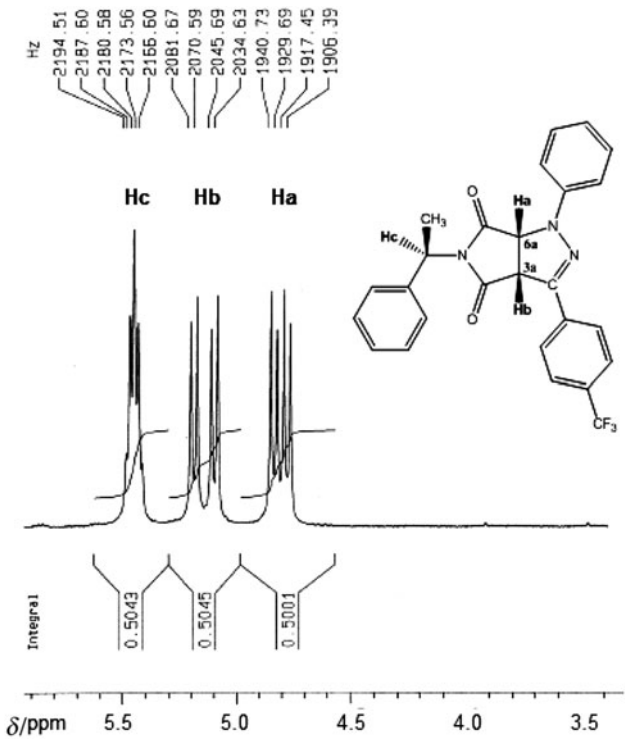


Fig. 1 Splitting patterns of the protons in **8f**

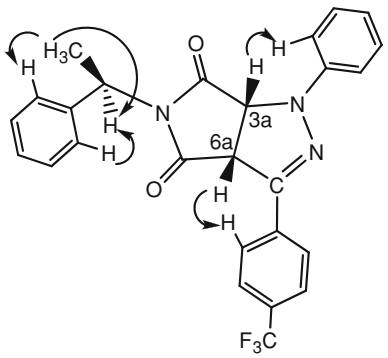


Fig. 2 ^{1}H NMR couplings in **8f**

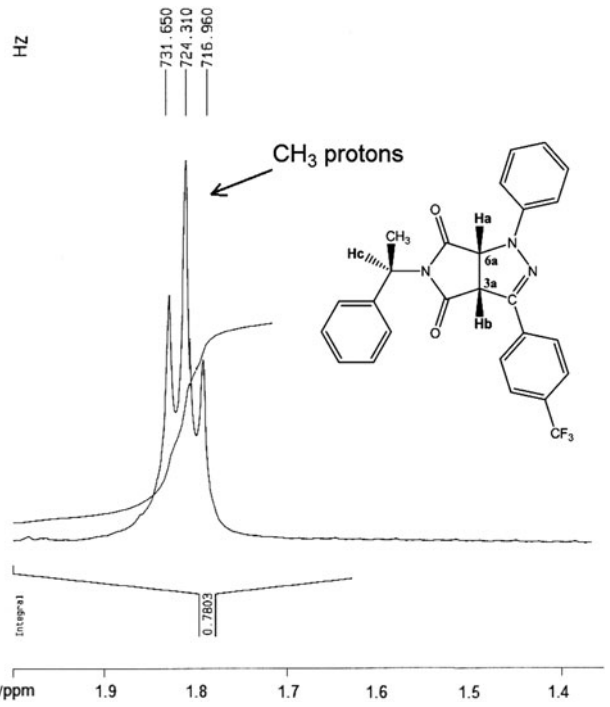


Fig. 3 ^{1}H NMR splitting of methyl protons on chiral carbon

centers by X-ray crystallography and regioisomeric ratios of some cycloadducts. The results of X-ray single-crystal diffraction measurements indicated that the compounds **7a/8a** and the compounds **7d/8d** were as a regioisomeric mixture in approximately 1:1 ratio (Figs. 4, 5). This result also revealed that these cycloaddition reactions are stereospecific due to formation of two regioisomers depending on the starting chiral maleimide with *R* configuration. In both structures depicted in Figs. 4 and 5, the C5 and N2 sites are disordered, with swapped identities, due to the mixture of inseparable diastereomers present in the crystals. Refined population parameters yielded 0.486(9) **7a**:0.514(9) **8a** and 0.428(2) **7d**:0.572(2) **8d**. The absolute configurations, which agreed with that of the starting materials, were determined from resonant scattering of light using Cu K_{α} radiation, using the Flack *X* and Hooft *Y* parameters [57, 58]: for **7a/8a**, $X = 0.2(2)$ and $Y = 0.11(9)$; for **7d/8d**, $X = 0.04(14)$ and $Y = 0.05(6)$. This corresponds to a probability of 1.000 that the depicted and expected configuration is correct in both cases.

The formation of a single regioisomer of the compounds **8f** and **7i** was demonstrated by their X-ray diffraction data (Fig. 6). According to these results, the cycloaddition reactions yielded the cycloadducts **8f** and **7i** as major product in fully regiocontrolled manner by the orientation of the unsymmetrical dipole [59]. Splitting patterns as a representative example of the protons attached to the chiral carbons in compound **8f** are shown in Fig. 7.

The ^{1}H NMR spectra of all new compounds showed two doublets at around 4.7 and 5.0 ppm, which were assigned to the protons at C–6a and C–3a, respectively. Chemical shifts and coupling constants are shown in Table 2. Electron-withdrawing or electron-releasing substituents on *para*-position of the phenyl ring attached to azomethine carbon caused slight shielding or deshielding effect on H_b bridge protons. However, the vicinal coupling constants have been shown to be diagnostic ($J_{trans} < 6$ Hz, $J_{cis} \approx 9$–12 Hz), so observed coupling constants for H_a and H_b protons are compatible with *cis*-configuration, as supported by the X-ray ORTEP views and previously reported literature values for similar stereochemistry

Scheme 4

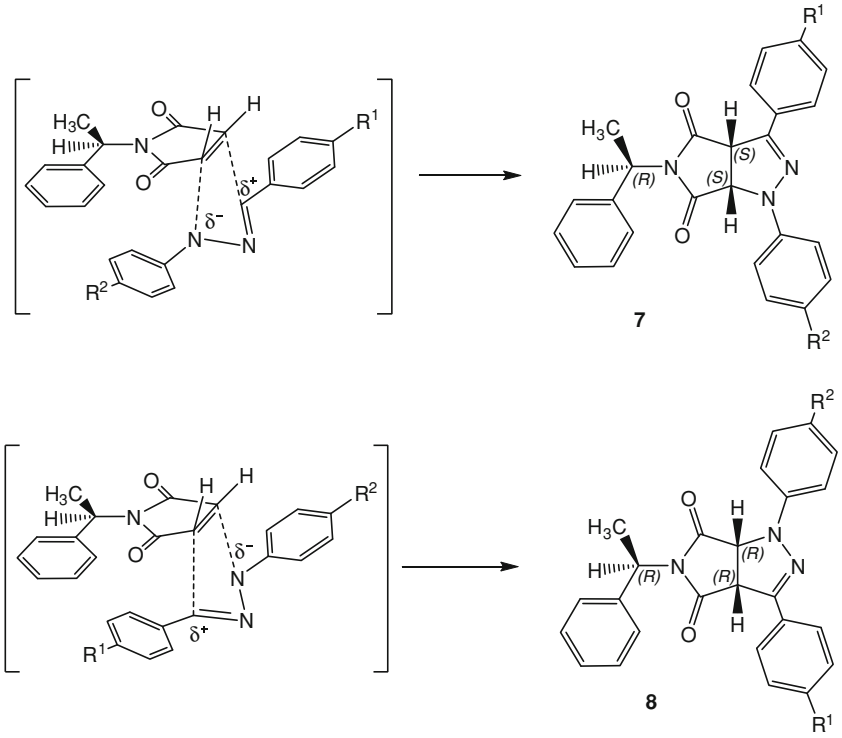
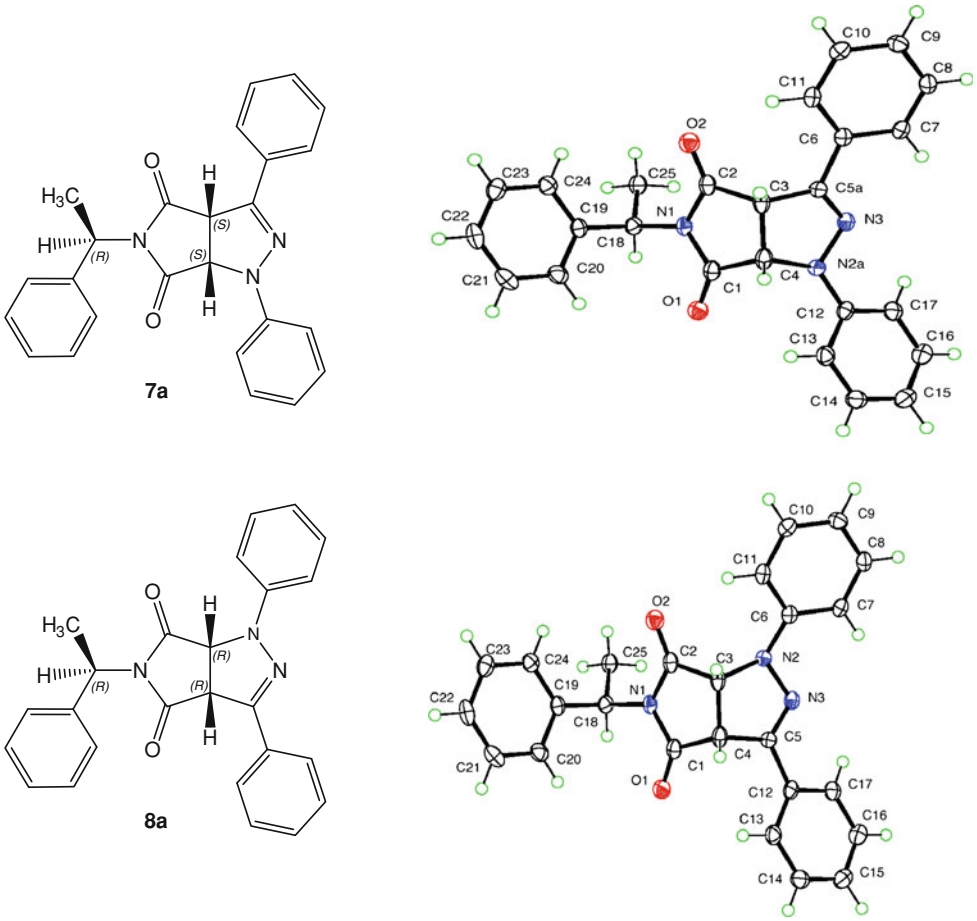


Fig. 4 Structures and X-ray ORTEP views of the regioisomers **7a** and **8a**



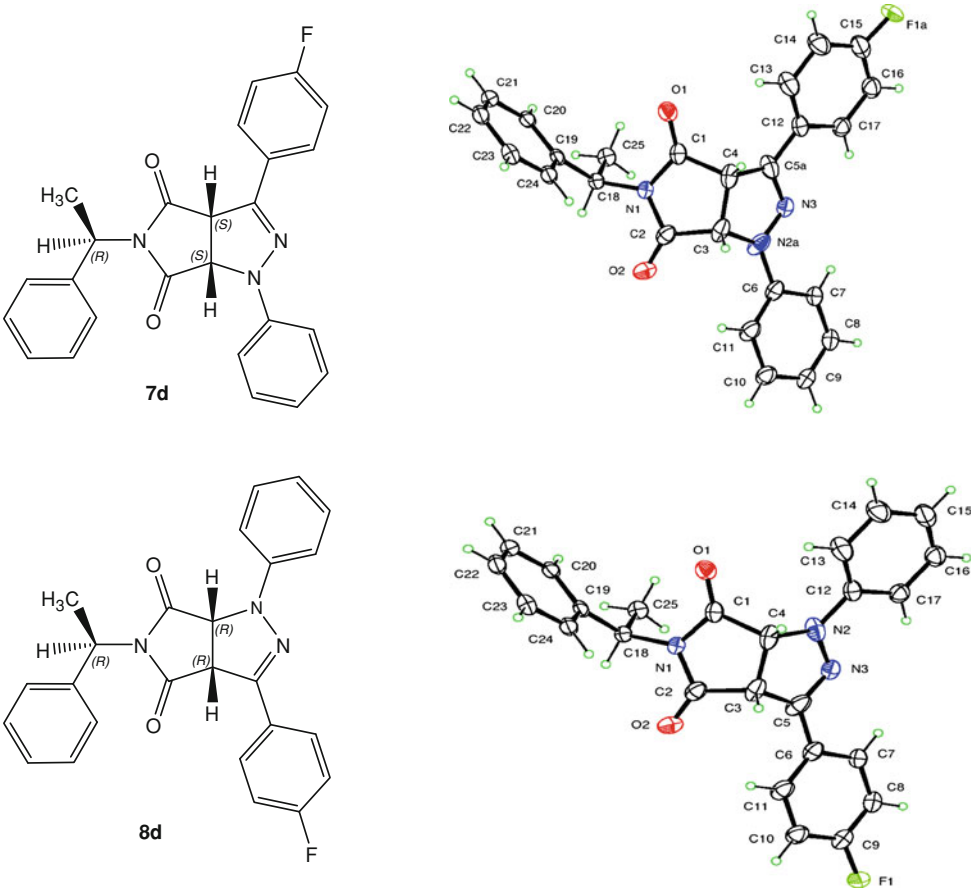


Fig. 5 Structures and X-ray ORTEP views of the regioisomers **7d** and **8d**

Table 1 Cycloaddition products **7a**–**8k** and reaction conditions

Comp.	R^1	R^2	Reaction conditions		Yield/%	$[\alpha]_D^{21}$ [a]	Regioisomeric ratio (**7**:**8**)
			Solvent	Time/h			
7a	H	H	Toluene	12	51	+80.0	50:50
7b	Cl	H	CH_3CN	20	84	+70.0	Inseparable mixture
7c	Br	H	CH_3CN	48	72	+60.0	Inseparable mixture
7d	F	H	CH_3CN	20	85	+60.0	57:43
7e	CN	H	CH_3CN	12	92	+68.0	Inseparable mixture
7f	CF_3	H	CH_3CN	8	70	+12.0	0:100
7g	OCH_3	H	CH_3CN	20	97	+40.0	Inseparable mixture
7h	SCH_3	H	CH_3CN	20	91	+44.0	Inseparable mixture
7i	$OCOCH_3$	H	CH_3CN	3	71	+79.0	100:0
7j	CH_3	CN	CH_3CN	12	96	+80.0	Inseparable mixture
7k	NO_2	Cl	CH_3CN	12	88	+53.0	Inseparable mixture

All reactions carried out at r.t.

[a] $c = 0.01$ g cm^{-3}, acetone

[60, 61]. The IR spectra of compounds **7a**–**8k** exhibited amide carbonyl absorption bands at around 1,705–1,710 cm^{-1}. The ^{13}C NMR spectra of all chiral products showed the signals corresponding to amide carbonyl carbons at around 170–174 ppm and the signals corresponding to C=N carbon at around 143–147 ppm.

In the electrospray ionization (EI) mass spectra of cycloadducts **7a**–**8k**, almost all cycloadducts displayed molecular ions as base peak. Only compounds **7g** and **7k** showed different fragmentation pattern and ionic species: M^+–$CH_3OC_6H_5C{=}NNC_6H_5$, which can be accounted for by retrocycloaddition of cycloadduct **7g**, and M^+–NO_2Cl,

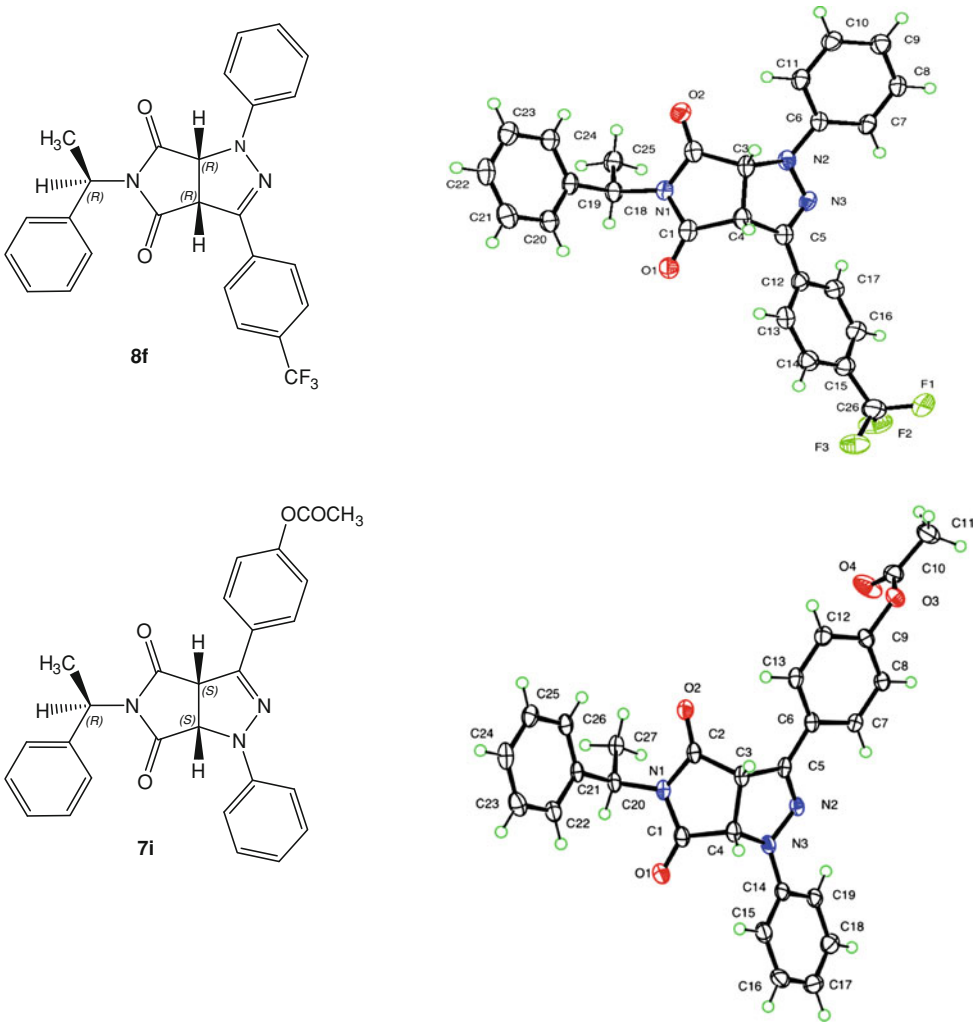


Fig. 6 Structures and X-ray ORTEP views of the regioisomers **8f** and **7i**

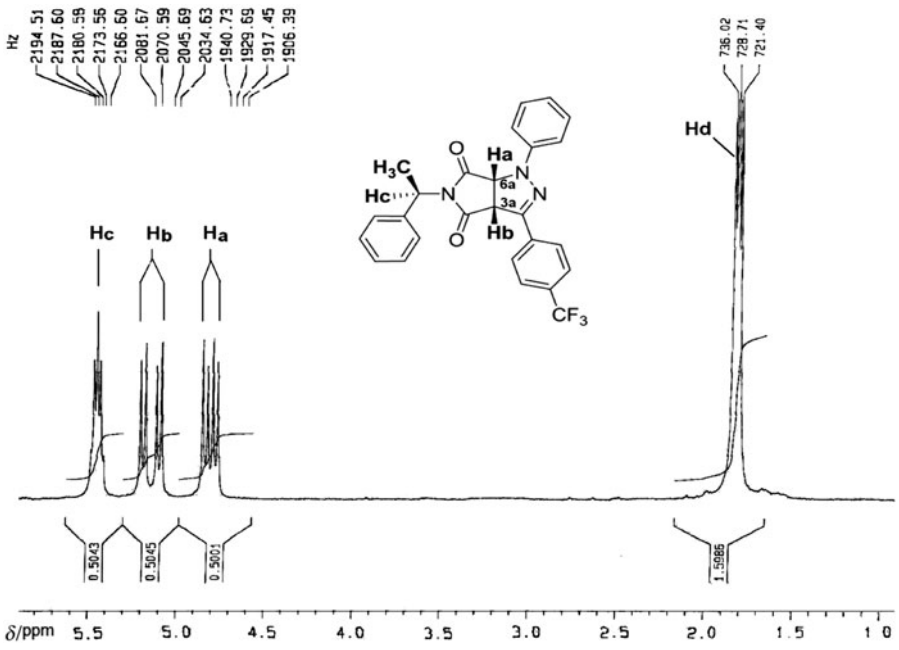
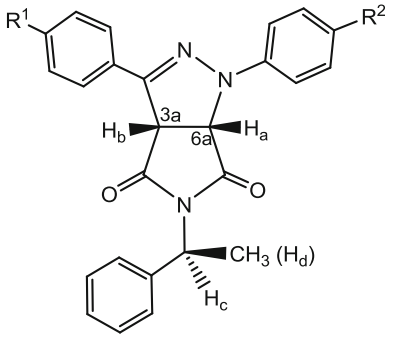


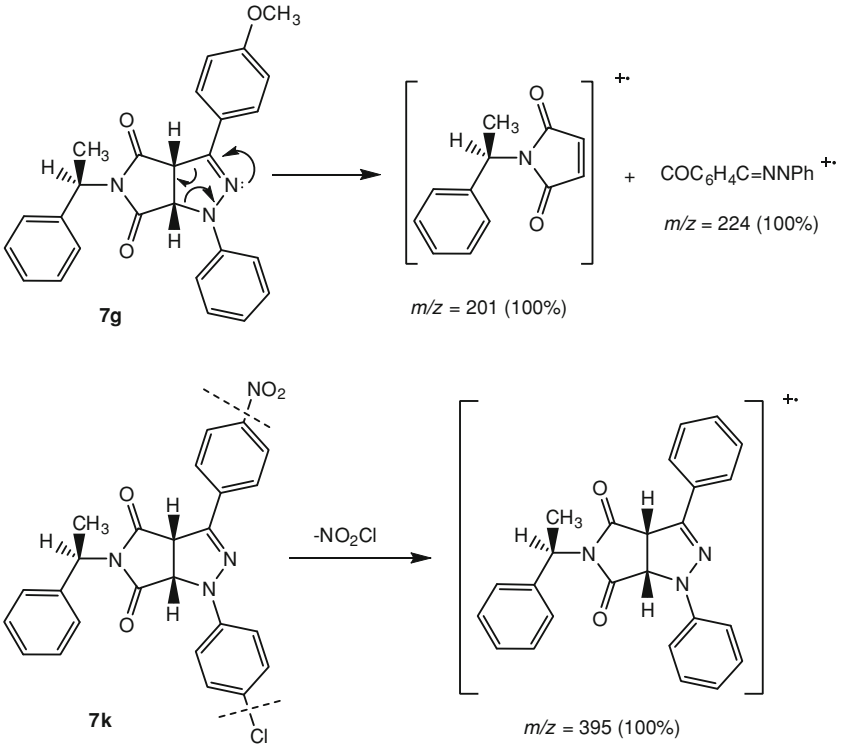
Fig. 7 Representative expanded ^{1}H NMR spectrum of compound **8f**, indicating splitting patterns of the aliphatic protons

Table 2 ^{1}H NMR chemical shifts and coupling constants for aliphatic protons of compounds **7a–8k** in $CDCl_3$



Comp.	H_c/ppm	*J*/Hz	H_b/ppm	*J*/Hz	H_a/ppm	*J*/Hz	H_d/ppm	*J*/Hz
7a	5.30, q	7.2	5.42, dd	10.8, 3.3	5.24, dd	10.8, 1.7	1.70, t	4.2
7b	5.44, t	7.0	5.01, dd	35.7, 10.9	4.70, dd	22.1, 10.9	1.80, t	7.2
7c	5.43, t	7.0	5.01, dd	34.8, 11.0	4.70, dd	22.9, 10.9	1.81, t	7.3
7d	5.44, quint	7.4	5.01, dd	34.6, 10.9	4.70, dd	20.9, 10.9	1.83, t	7.1
7e	5.44, quint	6.7	5.15, dd	32.2, 11.1	4.76, dd	20.1, 11.1	1.81, t	7.0
7f	5.37, quint	7.4	4.95, dd	33.4, 10.7	4.75, dd	24.1, 10.7	1.81, t	7.1
7g	5.43, quint	7.3	4.98, dd	32.7, 10.9	4.75, dd	24.4, 10.9	1.80, t	7.4
7h	5.44, t	7.1	4.95, dd	51.1, 10.9	4.70, dd	21.5, 11.0	1.80, t	6.8
7i	5.44, quint	7.0	5.08, dd	29.8, 11.0	4.76, dd	23.2, 11.0	1.82, t	7.3
7j	5.57, t	9.7	5.28–5.34, td	10.8, 3.3	Overlap with H_b signal	–	1.69, t	6.5
7k	5.42, quint	5.8	5.10, dd	29.7, 10.7	4.86, dd	23.2, 10.7	1.80, t	5.7

Scheme 5



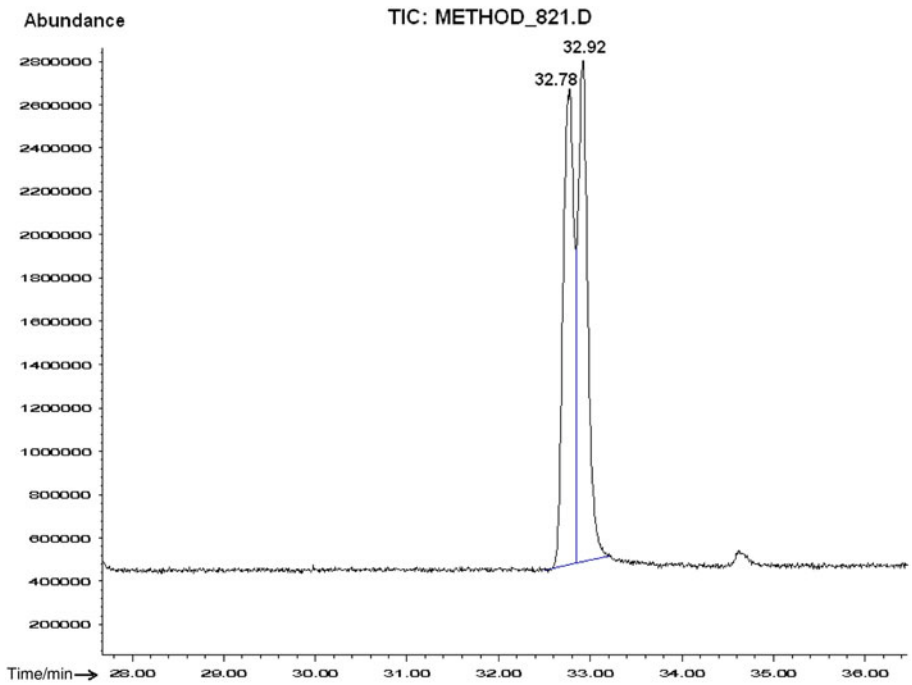


Fig. 8 Gas chromatogram of **7c**

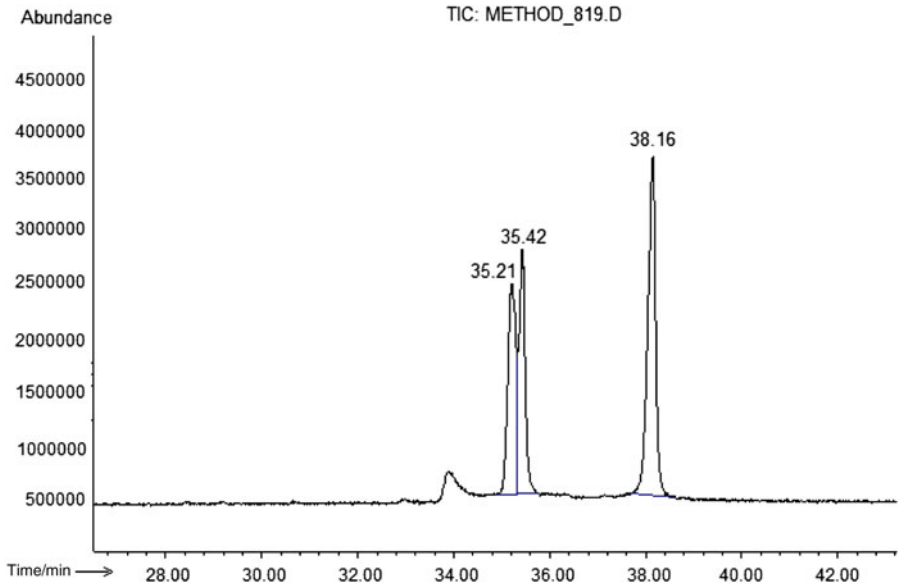


Fig. 9 Gas chromatogram of **7i**

by producing more stable unsubstituted pyrrolo[3,4-*c*]pyrazole-4,6-dione from cycloadduct **7k** (Scheme 5).

In the ^{13}C NMR spectra of the cycloadducts, among the aliphatic carbons the most deshielded one is 3a–C due to its proximity to two nitrogens, and it resonated at around 64–66 ppm for **7a**–**8k**. The signals of the carbonyl carbons were found at around 171–173 ppm and the azomethine C=N carbons at around 143–151 ppm.

Upon examination of the gas chromatograms of the pure samples of cycloadducts **7a**–**8k**, in some cases we observed two adjacent peaks which are almost fused, related to the diastereomers (regioisomers). A typical gas chromatogram of **7c/8c** is shown in Fig. 8. Mass spectra of the two isomeric compounds are the same.

In some cases, besides the GC peaks related to the stereoisomeric mixture, there was a third peak with two hydrogen atoms fewer, which can easily be attributed to the aromatization product on the GC column. We observed this peak in the gas chromatograms of **7i** and **7j** with relatively high abundance. A typical gas chromatogram of **7i**

indicating the above observation is shown in Fig. 9. The retention time peak at 38.16 min is possibly of aromatized product.

Conclusions

1,3-Dipolar cycloaddition of nitrilimines to chiral (1*R*)-*N*-(1-phenylethyl)maleimide gives rise to straightforward formation of cycloadducts as a regioisomeric mixture in good to excellent yields. In some cases, regioselectivity is very high, as much as 100% (e.g., **8f** and **7i**). Gas chromatograms of the cycloadducts clearly show the regioisomeric mixture and fully aromatized triazoles in some samples. Exact structures of the stereoisomers were determined by X-ray diffraction and NMR data.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on BRUKER and VARIAN spectrometers (200, 300, and 400 MHz for proton, and 75 and 100 MHz for carbon). IR spectra were recorded on a SHIMADZU FTIR-8400S instrument from KBr pellets. GC–MS spectra were run on an Agilent 6890 GC System 5973 MSD instrument. Optical rotations were measured by a Rudolph Research Analytical Autopol I automatic polarimeter using path length of 10 cm. Elemental analyses were performed on EuroVector EA 3000 and Elementar instruments and results agreed satisfactorily (±0.2%) with calculated values. A Chromatotron™ centrifugal thin-layer chromatograph system was used for purification and isolation of cycloadducts. Melting points were determined on a MELTEMP apparatus. Thin-layer chromatography (TLC) was done using precoated plates with fluorescent indicator (Merck 5735). Stain solutions of permanganate, *p*-anisaldehyde, and iodine were used for visualization of TLC spots.

(R)-N-(1-Phenylethyl)maleimide (**6**)

(*R*)-1-Phenylethylamine (**5**, 2.42 g, 20.0 mmol) was dissolved and stirred in 25 cm^3 acetone. Solution of 4.10 g maleic anhydride (42.0 mmol) in 25 cm^3 acetone was added dropwise over 15 min, and the resulting yellow solution was stirred at room temperature for 4 h. The reaction mixture was poured into 50 cm^3 ice-water to precipitate the white product. The precipitate was isolated by filtration and dried under vacuum to yield 73% (*R*,*E*)-4-oxo-4-(1-phenylethylamino)but-2-enoic acid, which was used in the next step without purification.

(*R*,*E*)-4-Oxo-4-(1-phenylethylamino)but-2-enoic acid (14.6 mmol), 1.43 g anhydrous sodium acetate (17.5 mmol), and 45 g (438 mmol) acetic anhydride were added into a three-necked flask. The yellow reaction mixture was heated to 95–100 °C for 3 h, and after cooling to room temperature, the brown reaction mixture was poured into 40 cm^3 ice-water mixture with stirring for 1 h. The reaction mixture was extracted with ethyl acetate (3 × 25 cm^3), and the combined ethyl acetate layers were dried over Na_2SO_4. Finally, the solvent was evaporated under reduced pressure, and the remaining orange oil was dried in vacuo and purified by column chromatography (ethyl acetate/*n*-hexane 1:3). (*R*)-(+)-*N*-(1-Phenylethyl)maleimide (**6**) was obtained as light-yellow oil (1.6 g, 54%); $[\alpha]_D^{21} = +88.7°$ ($c = 0.01$ g cm^{-3}, $CHCl_3$). Physical data were found to agree with those published for the (*S*)-enantiomer in Ref. [56].

General procedure for the synthesis of chiral dihydropyrrolo[3,4-c]pyrazolediones ***7a–8k***

The corresponding hydrazonyl chloride **4** (0.5 mmol) and maleimide **6** (0.5 mmol) were dissolved in 20 cm^3 dry acetonitrile. Et_3N (0.202 g, 2 mmol) was added dropwise into the mixture with stirring, and the reaction mixture was stirred at room temperature for 2–4 h. The progress of reaction was monitored by TLC. After the reaction was complete, all CH_3CN was evaporated, and the reaction mixture was mixed with 50 cm^3 water. The precipitated crude cycloadduct **7/8** was collected by suction filtration, washed with 50 cm^3 water and 25 cm^3 hexane, and dried in vacuo for 1–2 h. Finally, chiral cycloadducts **7/8** were purified with a Chromatotron (centrifugal thin-layer chromatograph) using *n*-hexane/ethyl acetate as eluent and recrystallized from appropriate solvent mixtures as indicated.

(3aS,6aS)- and (3aR,6aR)-5,6a-Dihydro-1,3-diphenyl-5-[(1R)-1-phenylethyl]pyrrolo[3,4-c]pyrazole-4,6(1H,3aH)-dione (**7a/8a**, $C_{25}H_{21}N_3O_2$)

Inseparable stereoisomers, detected by X-ray diffraction. Colorless plate crystals; yield 100 mg (51%); m.p.: 150–152 °C (acetone); $[\alpha]_D^{21} = +80.0°$ cm^3 g^{-1} dm^{-1} ($c = 0.01$ g cm^{-3}, acetone); $R_f = 0.75$ (ethyl acetate/*n*-hexane 1:2); IR (KBr): $\bar{\nu} = 3{,}483$, 3,059, 2,926 (C–H), 1,710 (C=O), 1,597 (C=N), 1,494, 1,386, 1,346, 1,222, 1,192, 754, 696 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 7.98$ (t, $J = 6.9$ Hz, 2H), 7.43–7.50 (m, 5H), 7.24–7.36 (m, 7H), 6.95 (q, $J = 7.3$ Hz, 1H), 5.42 (dd, $J = 10.8$, 3.3 Hz, 1H), 5.30 (q, $J = 7.2$ Hz, 1H), 5.24 (dd, $J = 10.8$, 1.7 Hz, 1H), 1.70 (t, $J = 4.2$ Hz, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 173.8$ (C=O), 172.8 (C=O), 145.0 (C=N), 144.5, 139.8, 131.0, 129.5, 128.9, 128.9, 128.8, 127.9, 127.5, 127.0, 121.0, 114.4, 66.0 (–CH), 54.0 (–CH), 50.3 (–CH), 16.8 (–CH_3) ppm; MS (70 eV): *m*/*z* (%) = 395 (100) [M]$^+$, 291 (65), 247 (40), 219 (25), 105 (20), 77 (20).

(3aS,6aS)-3-(4-Chlorophenyl)-5,6a-dihydro-1-phenyl-5-[(1R)-1-phenylethyl]pyrrolo[3,4-c]pyrazole-4,6(1H,3aH)-dione (**7b**, $C_{25}H_{20}ClN_3O_2$)

Light-yellow needle crystals; yield 181 mg (84%); m.p.: 189–191 °C (dichloromethane/*n*-hexane); $[\alpha]_D^{21} = +70.0°$ $cm^3\ g^{-1}\ dm^{-1}$ ($c = 0.01$ g cm^{-3}, acetone); $R_f = 0.76$ (ethyl acetate/*n*-hexane 1:2); IR (KBr): $\bar{\nu} = 3{,}470$, 3,090, 2,939 (C–H), 1,705 (C=O), 1,597 (C=N), 1,492, 1,379, 1,356, 1,220, 1,193, 831, 750, 696 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): $\delta = 8.01$ (d, $J = 8.0$ Hz, 2H), 7.58 (d, $J = 6.7$ Hz, 2H), 7.19–7.48 (m, 9H), 7.02 (t, $J = 6.5$ Hz, 1H), 5.44 (t, $J = 7.0$ Hz, 1H), 5.01 (dd, $J = 35.7$, 10.9 Hz, 1H), 4.70 (dd, $J = 22.1$, 10.9 Hz, 1H), 1.80 (t, $J = 7.2$ Hz, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 171.5$ (C=O), 170.5 (C=O), 144.5 (C=N), 142.3, 142.1, 139.0, 135.4, 129.3, 128.9, 128.8, 128.6, 128.3, 127.6, 121.7, 114.4, 65.3 (–CH), 53.1 (–CH), 51.5 (–CH), 16.3 ($–CH_3$) ppm; MS (70 eV): *m/z* (%) = 429 (100) $[M]^+$, 325 (82), 281 (35), 253 (29), 105 (35), 77 (29).

(3aS,6aS)-3-(4-Bromophenyl)-5,6a-dihydro-1-phenyl-5-[(1R)-1-phenylethyl]pyrrolo[3,4-c]pyrazole-4,6(1H,3aH)-dione (**7c**, $C_{25}H_{20}BrN_3O_2$)

Light-yellow crystals; yield 170 mg (72%); m.p.: 146–148 °C (acetone); $[\alpha]_D^{21} = +60.0°$ $cm^3\ g^{-1}\ dm^{-1}$ ($c = 0.01$ g cm^{-3}, acetone); $R_f = 0.76$ (ethyl acetate/*n*-hexane 1:2); IR (KBr): $\bar{\nu} = 3{,}471$, 3,032, 2,939 (C–H), 1,708 (C=O), 1,599 (C=N), 1,573, 1,491, 1,379, 1,356, 1,193, 750, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.93$ (d, $J = 8.5$ Hz, 2H), 7.57 (q, $J = 4.0$ Hz, 4H), 7.46 (t, $J = 6.4$ Hz, 2H), 7.28–7.39 (m, 5H), 7.02 (t, $J = 7.2$ Hz, 1H), 5.43 (t, $J = 7.0$ Hz, 1H), 5.01 (dd, $J = 34.8$, 11.0 Hz, 1H), 4.70 (dd, $J = 22.9$, 10.9 Hz, 1H), 1.81 (t, $J = 7.3$ Hz, 3H) ppm; ^{13}C NMR (100 MHz,$CDCl_3$): $\delta = 172.3$ (C=O), 171.5 (C=O), 144.3 (C=N), 141.8, 138.7, 131.7, 129.4, 129.2, 128.6, 128.5, 128.2, 127.6, 123.7, 121.7, 114.4, 65.3 (–CH), 53.1 (–CH), 51.5 (–CH), 16.3 ($–CH_3$) ppm; MS (70 eV): *m/z* (%) = 473 (100) $[M]^+$, 369 (74), 327 (32), 299 (29), 247 (15), 105 (53), 77 (47).

(3aS,6aS)- and (3aR,6aR)-3-(4-Fluorophenyl)-5,6a-dihydro-1-phenyl-5-[(1R)-1-phenylethyl]pyrrolo[3,4-c]pyrazole-4,6(1H,3aH)-dione (**7d/8d**, $C_{25}H_{20}FN_3O_2$)

Inseparable stereoisomers, detected by X-ray diffraction. White crystals; yield 175 mg (85%); m.p.: 205–206 °C (dichloromethane/*n*-pentane); $[\alpha]_D^{21} = +60.0°$ $cm^3\ g^{-1}\ dm^{-1}$ ($c = 0.01$ g cm^{-3}, acetone); $R_f = 0.75$ (ethyl acetate/*n*-hexane 1:2); IR (KBr): $\bar{\nu} = 3{,}481$, 3,061, 2,980 (C–H), 2,941, 1,708 (C=O), 1,597 (C=N), 1,498, 1,379, 1,356, 1,224, 1,193, 1,128, 750, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.07$ (t, $J = 3.1$ Hz, 2H), 7.58 (d, $J = 7.2$ Hz, 2H), 7.47 (t, $J = 6.8$ Hz, 2H), 7.28–7.37 (m, 5H), 7.13–7.22 (m, 2H), 7.02 (t, $J = 7.0$ Hz, 1H), 5.44 (quintet, $J = 7.4$ Hz, 1H), 5.01 (dd, $J = 34.6$, 10.9 Hz, 1H), 4.70 (dd, $J = 20.9$, 10.9 Hz, 1H), 1.83 (t, $J = 7.1$ Hz, 3H) ppm; ^{13}C NMR (100 MHz,$CDCl_3$): $\delta = 172.5$ (C=O), 171.5 (C=O), 144.6 (C=N), 142.0, 138.7, 129.2, 129.1, 129.0, 128.6, 128.2, 127.6, 121.5, 115.8, 115.6, 114.4, 65.4 (–CH), 53.3 (–CH), 51.5 (–CH), 16.3 ($–CH_3$) ppm; MS (70 eV): *m/z* (%) = 413 (100) $[M]^+$, 309 (78), 265 (35),105 (29), 70 (21).

4-[(3aS,6aS)-1,3a,4,5,6,6a-Hexahydro-4,6-dioxo-1-phenyl-5-[(1R)-1-phenylethyl]pyrrolo[3,4-c]pyrazol-3-yl]benzonitrile (**7e**, $C_{26}H_{20}N_4O_2$)

Yellow powder; yield 194 mg (92%); m.p.: 207–209 °C; $[\alpha]_D^{21} = +68.0°$ $cm^3\ g^{-1}\ dm^{-1}$ ($c = 0.01$ g cm^{-3}, acetone); $R_f = 0.7$ (ethyl acetate/*n*-hexane 1:2); IR (KBr): $\bar{\nu} = 3{,}398$, 3,059, 2,941 (C–H), 2,225 (C≡N), 1,712 (C=O), 1,597 (C=N), 1,496, 1,384, 1,356, 1,220, 1,193, 750, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.15$ (d, $J = 7.1$ Hz, 2H), 7.70 (d, $J = 8.1$ Hz, 2H), 7.60 (d, $J = 5.7$ Hz, 2H), 7.45 (t, $J = 6.5$ Hz, 2H), 7.30–7.41 (m, 5H), 7.06 (t, $J = 7.2$ Hz, 1H), 5.44 (quintet, $J = 6.7$ Hz, 1H), 5.15 (dd, $J = 32.2$, 11.1 Hz, 1H), 4.76 (dd, $J = 20.1$, 11.1 Hz, 1H), 1.81 (t, $J = 7.0$ Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 171.9$ (C=O), 171.3 (C=O), 143.5 (C=N), 140.7, 138.5, 134.7, 132.3, 129.3, 128.7, 128.3, 127.6, 127.2, 122.3, 118.8, 114.6, 112.1, 65.4 (–CH), 52.7 (–CH), 51.6 (–CH), 16.4 ($–CH_3$) ppm; MS (70 eV): *m/z* (%) = 420 (100) $[M]^+$, 316 (78), 272 (25), 244 (16), 105 (33), 70 (38).

(3aR,6aR)-5,6a-Dihydro-1-phenyl-5-[(1R)-1-phenylethyl]-3-[4-(trifluoromethyl)phenyl]pyrrolo[3,4-c]pyrazole-4,6(1H,3aH)-dione (**8f**, $C_{26}H_{20}F_3N_3O_2$)

Light-green crystals; yield 161 mg (70%); m.p.: 174–176 °C (acetic acid); $[\alpha]_D^{21} = +12.0°$ $cm^3\ g^{-1}\ dm^{-1}$ ($c = 0.01$ g cm^{-3}, acetone); $R_f = 0.68$ (ethyl acetate/*n*-hexane 1:2); IR (KBr): $\bar{\nu} = 3{,}452$, 3,064, 2,941 (C–H), 1,708 (C=O), 1,599 (C=N), 1,500, 1,327, 1,193, 1,166, 1,068, 844, 750, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.17$ (q, $J = 3.8$ Hz, 2H), 7.70 (t, $J = 4.7$ Hz, 2H), 7.61 (t, $J = 7.6$ Hz, 2H), 7.47 (t, $J = 6.5$ Hz, 2H), 7.28–7.41 (m, 5H), 7.05 (t, $J = 7.0$ Hz, 1H), 5.44 (quintet, $J = 7.0$ Hz, 1H), 5.08 (dd, $J = 29.8$, 11.0 Hz, 1H), 4.76 (dd, $J = 23.2$, 11.0 Hz, 1H), 1.82 (t, $J = 7.3$ Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 172.1$ (C=O), 171.4 (C=O), 143.9 (C=N), 141.2, 138.6, 133.8, 130.9, 129.3, 128.6, 128.3, 127.6, 127.1, 125.5 ($–CF_3$), 122.6, 121.9, 114.5 (CF_3), 65.3 (–CH, 3aC), 52.9 ($–CH_3CH$), 51.6 (–CH, 6aC), 16.4 ($–CH_3$) ppm; MS (70 eV): *m/z* (%) = 463 (100) $[M]^+$, 359 (80), 315 (30), 269 (10), 105 (40), 70 (43).

(3aS,6aS)-5,6a-Dihydro-3-(4-methoxyphenyl)-1-phenyl-5-[(1R)-1-phenylethyl]pyrrolo[3,4-c]pyrazole-4,6(1H,3aH)-dione (**7g**, $C_{26}H_{23}N_3O_3$)

Light-yellow needles; yield 209 mg (97%); m.p.: 135–137 °C (dichloromethane/*n*-hexane); $[\alpha]_D^{21} = +40.0°$ $cm^3\ g^{-1}\ dm^{-1}$ ($c = 0.01$ g cm^{-3}, acetone); $R_f = 0.75$ (ethyl acetate/

n-hexane 1:2); IR (KBr): $\bar{\nu}$ = 3,487, 3,056, 2,935 (C–H), 2,837, 1,708 (C=O), 1,597 (C=N), 1,496, 1,379, 1,356, 1,253, 1,176, 835, 750, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.01 (t, J = 6.3 Hz, 1H), 7.59 (d, J = 7.3 Hz, 2H), 7.46 (q, J = 7.6 Hz, 2H), 7.20–7.35 (m, 5H), 6.98 (d, J = 8.0 Hz, 3H), 6.64 (s, 1H), 5.37 (quintet, J = 7.4 Hz, 1H), 4.95 (dd, J = 33.4, 10.7 Hz, 1H), 4.75 (dd, J = 24.1, 10.7 Hz, 1H), 3.80 (s, 3H), 1.81 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz,$CDCl_3$): δ = 172.7 (C=O), 171.7 (C=O), 160.8, 145.0 (C=N), 142.9, 134.0, 129.2, 128.8, 128.5, 128.1, 127.7, 127.2, 123.1, 121.2, 114.3, 65.3 (–CH, 3aC), 55.4 (OCH_3), 53.4 (–CH), 51.4 (–CH), 16.4 ($–CH_3$) ppm; MS (70 eV): *m/z* (%) = 201(100) $[M]^+$–$C_{16}H_5N$–N=C–$C_6H_4OCH_3$, 158 (25), 104 (40), 77 (40), 51 (15).

(3aS,6aS)-5,6a-Dihydro-3-[4-(methylthio)phenyl]-1-phenyl-5-[(1R)-1-phenylethyl]pyrrolo[3,4-c]pyrazole-4,6(1H,3aH)-dione (**7h**, $C_{26}H_{23}N_3O_2S$)
Light-yellow crystals; yield 200 mg (91%); m.p.: 82–84 °C (dichloromethane/*n*-pentane); $[\alpha]_D^{21}$ = +44.0° $cm^3\ g^{-1}\ dm^{-1}$ (c = 0.01 g cm^{-3}, acetone); R_f = 0.80 (ethyl acetate/*n*-hexane 1:2); IR (KBr): $\bar{\nu}$ = 3,483, 3,056, 2,980, 2,920 (C–H), 1,708 (C=O), 1,597 (C=N), 1,494, 1,388, 1,356, 1,226, 1,093, 750, 696 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 7.95–7.99 (m, 2H), 7.58 (q, J = 4.0 Hz, 2H), 7.46 (t, J = 6.5 Hz, 2H), 7.28–7.38 (m, 7H), 7.01 (t, J = 7.2 Hz, 1H), 5.43 (quintet, J = 7.3 Hz, 1H), 4.98 (dd, J = 32.7, 10.9 Hz, 1H), 4.75 (dd, J = 24.4, 10.9 Hz, 1H), 2.53 (s, 3H), 1.80 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.5 (C=O), 171.6 (C=O), 144.6 (C=N), 142.6, 140.7, 134.0, 129.2, 128.6, 128.2, 127.6, 127.4, 127.2, 125.8, 121.4, 114.3, 65.2 (–CH, 3aC), 53.2 (–CH), 51.4 (–CH), 16.4 ($–CH_3$), 15.3 ($–SCH_3$) ppm; MS (70 eV): *m/z* (%) = 441 (100) $[M]^+$, 337 (65), 295 (22), 266 (45), 250 (33), 105 (22), 70 (15).

(3aS,6aS)-3-[4-(Acetyloxy)phenyl]-5,6a-dihydro-1-phenyl-5-[(1R)-1-phenylethyl]pyrrolo[3,4-c]pyrazole-4,6(1H,3aH)-dione (**7i**, $C_{27}H_{23}N_3O_4$)
Yellow needle crystals; yield 160 mg (71%); m.p.: 86–88 °C (dichloromethane/*n*-hexane/acetone); $[\alpha]_D^{21}$ = +79.0° $cm^3\ g^{-1}\ dm^{-1}$ (c = 0.01 g cm^{-3}, acetone); R_f = 0.60 (ethyl acetate/*n*-hexane 1:2); IR (KBr): $\bar{\nu}$ = 3,412, 3,063, 2,937 (C–H), 1,757 (C=O), 1,710 (C=O), 1,599 (C=N), 1,498, 1,452, 1,357, 1,197, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.10 (q, J = 3.8 Hz, 2H), 7.58 (t, J = 7.6 Hz, 2H), 7.47 (t, J = 7.2 Hz, 2H), 7.24–7.36 (m, 5H), 7.18 (q, J = 4.6 Hz, 2H), 7.01 (t, J = 7.3 Hz, 1H), 5.44 (t, J = 7.1 Hz, 1H), 4.95 (dd, J = 51.1, 10.9 Hz, 1H), 4.70 (dd, J = 21.5,11.0 Hz, 1H), 2.35 (s, 3H) 1.80 (t, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.4 (C=O), 171.5 (C=O), 169.4 (C=O), 151.5 (C=N), 144.5, 142.0, 138.7, 129.2, 128.9, 128.6, 128.3, 128.2, 127.6, 121.8, 121.5, 114.4, 65.4 (–CH), 53.3 (–CH), 51.4 (–CH), 21.1($–CH_3$), 16.4 ($–CH_3$) ppm; MS (70 eV): *m/z* (%) = 453 (100) $[M]^+$, 411 (65), 307 (100), 236 (50), 207 (10), 105 (33), 70 (10).

4-[(3aS,6aS)-4,5,6,6a-Tetrahydro-3-(4-methylphenyl)-4,6-dioxo-5-[(1R)-1-phenylethyl]pyrrolo[3,4-c]pyrazol-1(3aH)-yl]benzonitrile (**7j**, $C_{27}H_{22}N_4O_2$)
White needle crystals; yield 213 mg (96%); m.p.: 234–236 °C (ethanol/*n*-hexane/acetone/dichloromethane); $[\alpha]_D^{21}$ = +80.0° $cm^3\ g^{-1}\ dm^{-1}$ (c = 0.01 g cm^{-3}, acetone); R_f = 0.58 (ethyl acetate/*n*-hexane 1:2); IR (KBr): $\bar{\nu}$ = 3,470, 3,032, 2,980, 2,941 (C–H), 2,218 (C≡N), 1,712 (C=O), 1,602 (C=N), 1,508, 1,390, 1,186, 829, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.96 (dd, J = 3.5, 4.6 Hz, 2H), 7.60 (s, 4H), 7.44 (t, J = 6.9 Hz, 2H), 7.26–7.36 (m, 5H), 5.42 (quintet, J = 5.8 Hz, 1H), 5.10 (dd, J = 29.7, 10.7 Hz, 1H), 4.86 (dd, J = 23.2, 10.7 Hz, 1H), 2.41 (s, 3H), 1.80 (t, J = 5.7 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.5 (C=O), 171.5 (C=O), 147.5 (C=N), 146.0, 142.0, 139.0, 133.5, 129.5, 128.7, 127.6, 127.5, 127.4, 120.0, 114.2, 103.0, 64.5 (–CH), 54.0 (–CH), 51.5 (–CH), 22.0 ($–CH_3$), 16.0 ($–CH_3$) ppm; MS (70 eV): *m/z* (%) = 434 (100) $[M]^+$, 330 (78), 286 (53), 105 (46), 70 (23).

(3aS,6aS)-1-(4-Chlorophenyl)-5,6a-dihydro-3-(4-nitrophenyl)-5-[(1R)-1-phenylethyl]pyrrolo[3,4-c]pyrazole-4,6(1H,3aH)-dione (**7k**, $C_{25}H_{19}ClN_4O_4$)
Orange powder; yield 210 mg (88%); m.p.: 242–244 °C; $[\alpha]_D^{21}$ = +53.0° $cm^3\ g^{-1}\ dm^{-1}$ (c = 0.01 g cm^{-3}, acetone); R_f = 0.62 (ethyl acetate/*n*-hexane 1:2); IR (KBr): $\bar{\nu}$ = 3,475, 3,057, 2,935 (C–H), 1,708 (C=O), 1,593 (C=N), 1,550, 1,492, 1,392, 1,334, 1,222, 1,195, 852, 690 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 8.32 (q, J = 4.5 Hz, 2H), 8.20 (t, J = 7.6 Hz, 2H), 7.53 (t, J = 8.8 Hz, 2H), 7.42 (q, J = 4.5 Hz, 2H), 7.24–7.29 (m, 5H), 5.57 (t, J = 9.7 Hz, 1H), 5.28–5.34 (td, J = 10.8, 3.3 Hz, 2H), 1.69 (t, J = 6.5 Hz, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 173.5 (C=O), 172.5 (C=O), 147.5 (C=N), 143.0, 142.5, 139.7, 137.0, 129.4, 128.9, 128.2, 128.0, 127.1, 125.6, 124.2, 116.3, 65.9 (–CH), 53.8 (–CH), 50.6 (–CH), 16.8 ($–CH_3$) ppm; MS (70 eV): *m/z* (%) = 395 (100) $[M]^+$–NO_2Cl, 291 (70), 247 (40), 218 (25), 105 (20), 70 (10).

X-ray crystallographic data

X-ray diffraction crystallographic data for the structural analysis of compounds **7a/8a** (CCDC 789119) and **7d/8d** (CCDC 789120) have been deposited with the Cambridge Crystallographic Data Center. Copies of this information can be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-

1223-336033; e-mail: deposit@ccdc.cam.ac.uk or http://ccdc.cam.ac.uk).

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