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1,3-DIPOLAR CYCLOADDITIONS OF 5-(4-METHOXYPHENYL)- AND 5-(1*H*-INDOL-3-YL)-SUBSTITUTED (1*Z*,4*R**,5*R**)-1-(ARYLMETHYLIDENE)-4-BENZAMIDO-3-OXOPYRAZOLIDIN-1-IUM-2-IDES TO OLEFINIC DIPOLAROPHILES

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Dedicated to Dr. Alfred Bader, the founder of Aldrich Chemical Company, on the occasion of his 85th birthday.

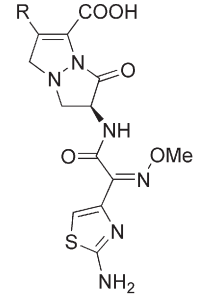
1,3-Dipolar cycloadditions of (1*Z*,4*R**,5*R**)-1-(arylmethylidene)-4-benzamido-5-(4-methoxyphenyl)-3-oxopyrazolidin-1-ium-2-ides **6a**–**6f** and their 5-(1*H*-indol-3-yl) analogues **6g**–**6j** to olefinic dipolarophiles **7**–**9** were studied. Stereochemistry was controlled by the structure of dipoles **6** and dipolarophiles **7**–**9**. Reactions of *ortho*-unsubstituted dipoles **6a**–**6c**, **6g** gave the major isomers **10** and **14** with *syn*-oriented protons H-3 and H-5, whilst *ortho*-disubstituted dipoles **6d**, **6e**, **6j** gave cycloadducts **11** and **12** with *anti*-oriented protons H-3 and H-5. In comparison with their 5-phenyl-substituted analogues, dipoles **6a**–**6e**, **6g**, **6j** were less reactive in cycloadditions to olefinic dipolarophiles **7**–**9**. This was reflected in longer reaction times, lower yields, and sometimes in lower selectivity as well. The relative configurations of cycloadducts were determined by NMR.

Keywords: Azomethine imides; 1,3-Dipolar cycloadditions; Cyclisations; Pyrazolidinones; Synthetic methods; NMR spectroscopy.

1,3-Dipolar cycloadditions are powerful methods for the preparation of five-membered heterocycles, since they enable access to polyfunctionalized chiral compounds with multiple asymmetric centres, usually with excellent stereocontrol[1]. Within this context, several examples of asymmetric cycloadditions in cyclic chiral azomethine imide series have also been reported. Generally, these reactions were accompanied by high facial and *endo*/*exo*-selectivity and afforded the corresponding fused dihydropyrazoles with a bridgehead N–N structural element[2–14].

6-Amino-7-oxohexahydropyrazolo[1,2-*a*]pyrazole-1-carboxylic acid is a useful heterocyclic scaffold for the preparation of heterocyclic conformationally constrained peptide mimetics and biologically active compounds[15]. For example, such pyrazolo[1,2-*a*]pyrazolone structural unit is a constituent of Eli-Lilly's γ-lactam antibiotics LY 186826, LY 193239, and LY 255262 (Fig. 1)[4,15].

In this context, we have previously reported 1,3-dipolar cycloadditions of (1*Z*,4*R**,5*R**)-1-(arylmethylidene)-4-benzamido-3-oxo-5-phenylpyrazolidin-1-ium-2-ides to various dipolarophiles with emphasis on regioselectivity and stereoselectivity of these cycloadditions[6,10–14,16,17]. Stereochemistry of these reactions was controlled by the stereodirecting phenyl group at position 5 in the chiral dipole, by the *ortho*-substituents at the 1′-Ar group, and by the structure of the dipolarophile[6,10–14]. Stereoselective combinatorial cycloadditions of these azomethine imides to maleimides[11] and β-keto esters[12] have also been reported. These cycloadditions enable an easy access to pyrazolo[1,2-*a*]pyrazolones as heterocyclic dipeptide analogues with variable amino acid sequence and stereochemistry. However, all previous cycloadditions of (1*Z*,4*R**,5*R**)-4-benzamido-3-oxo-5-phenylpyrazolidin-1-ium-2-ides gave heterocyclic dipeptides with 3-phenylalanine as the N-terminal amino acid. In continuation, we were interested in preparation of various 5-substituted 4-acylaminopyrazolidin-3-one azomethine imides, since their cycloadditions would lead to pyrazolo[1,2-*a*]pyrazolidinone-based dipeptides with N-terminal amino acids other than 3-phenylalanine. Herein, we report the results of a preliminary study on preparation of a se-



LY 186826 (R = COMe)
LY 193239 (R = SO_2Me)
LY 255262 (R = CN)

FIG. 1
Structures of γ-lactam antibiotics

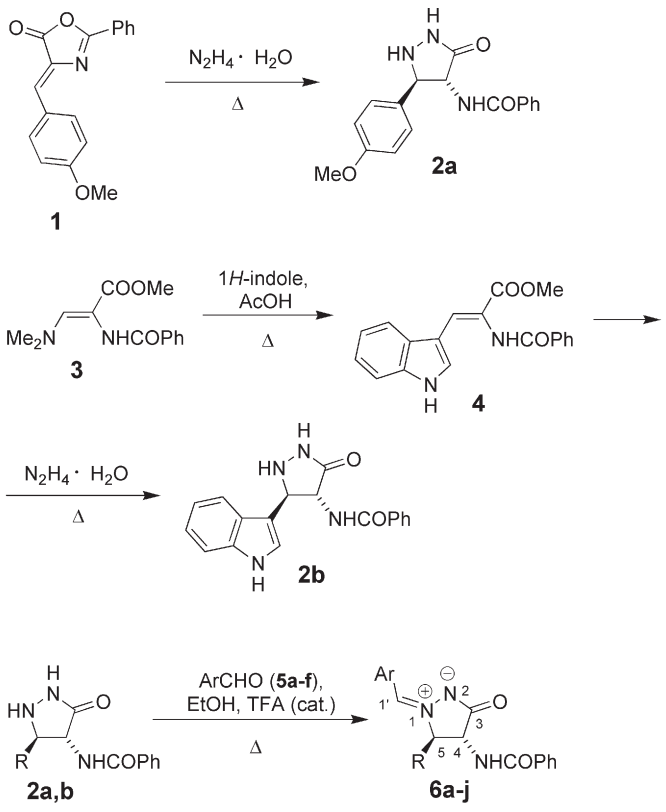
ries of novel azomethine imides **6a**–**6j** from aromatic aldehydes **5a**–**5f** and (4*R**,5*R**)-4-benzamido-5-(4-methoxyphenyl)pyrazolidin-3-one (**3a**) and (4*R**,5*R**)-4-benzamido-5-(1*H*-indol-3-yl)pyrazolidin-3-one (**3b**) as well as some 1,3-dipolar cycloadditions of dipoles **6a**–**6e**, **6g**, **6j** to dimethyl maleate (**7**), dimethyl fumarate (**8**), and methyl acrylate (**9**).

RESULTS AND DISCUSSION

(4*R**,5*R**)-4-Benzamido-5-(4-methoxyphenyl)pyrazolidin-3-one (**2a**) was prepared from azlactone **1** following the literature procedure[18]. (4*R**,5*R**)-4-Benzamido-5-(1*H*-indol-3-yl)pyrazolidin-3-one (**2b**) was obtained in two steps from methyl (*Z*)-2-benzamido-3-(dimethylamino)propenoate (**3**)[19,20]. First, enamino ester **3** was treated with 1*H*-indole in acetic acid according to the literature procedure[19] to give methyl 2-benzamido-3-(1*H*-indol-3-yl)-propenoate (**4**). Further treatment of 2,3-didehydrotryptophan ester **4** with excess hydrazine hydrate furnished pyrazolidinone **2b** in 71% yield. Pyrazolidinones **2a**, **2b** were then transformed with aromatic aldehydes **5a**–**5f** into the corresponding azomethine imides **6a**–**6j** under standard reaction conditions[6], i.e. in refluxing ethanol in the presence of catalytic amounts of trifluoroacetic acid. In this manner, dipoles **6a**–**6j** were prepared in 41–97% yields (Scheme 1, Table I).

TABLE I
Selected experimental data for pyrazolidinones **3** and azomethine imides **6**

Reaction	R	Ar	Yield, %
1→2a	4-methoxyphenyl	–	83
3→2b	1*H*-indol-3-yl	–	71
5a→6a	4-methoxyphenyl	Ph	91
5b→6b	4-methoxyphenyl	4-nitrophenyl	97
5c→6c	4-methoxyphenyl	3,4,5-trimethoxyphenyl	83
5d→6d	4-methoxyphenyl	2,4,6-trimethylphenyl	85
5e→6e	4-methoxyphenyl	2,6-dichlorophenyl	95
5f→6f	4-methoxyphenyl	2,4-dichlorophenyl	97
5a→6g	1*H*-indol-3-yl	Ph	77
5b→6h	1*H*-indol-3-yl	4-nitrophenyl	41
5d→6i	1*H*-indol-3-yl	2,4,6-trimethylphenyl	70
5e→6j	1*H*-indol-3-yl	2,6-dichlorophenyl	82

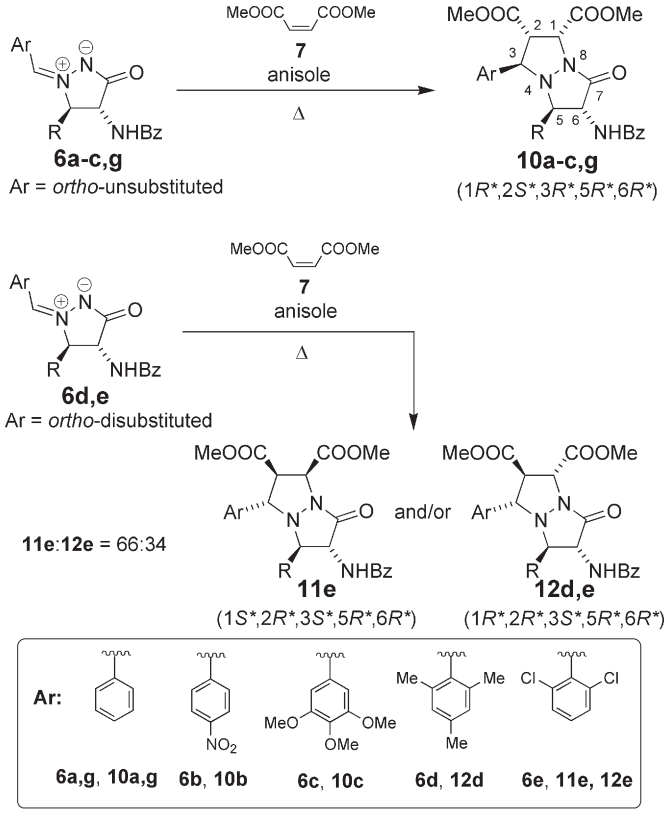


SCHEME 1

Next, 1,3-dipolar cycloadditions of azomethine imides **6** to olefinic dipolarophiles **7**–**9** in anisole under reflux were studied. Based on our previous observations in the (1*Z*,4*R**,5*R**)-1-(arylmethylidene)-4-benzamido-3-oxo-5-phenylpyrazolidin-1-ium-2-ide series[10–12], we carried out reactions only with combinations of dipoles **6** (with respect to the *ortho*-substituents at the 1′-Ar group) and dipolarophiles **7**–**9**, which proceeded selectively in the 5-phenyl series[10–12]. Thus, dimethyl fumarate (**8**) was reacted with *ortho*-disubstituted dipoles, methyl acrylate (**9**) with *ortho*-unsubstituted dipoles, and dimethyl maleate (**7**) with both types of dipoles.

Reactions of *ortho*-unsubstituted azomethine imides **6a**–**6c**, **6g** with dimethyl maleate (**7**) were stereoselective and furnished dimethyl (1*R**,2*S**,3*R**,5*R**,6*R**)-6-benzamido-3,5-diaryl-7-oxohexahydropyrazolo-[1,2-*a*]pyrazole-1,2-dicarboxylates **10a**–**10c**, **10g** in 21–69% yields. Simi-

larly, the reaction of *ortho*-disubstituted azomethine imide **6d** with dimethyl maleate (**7**) was selective and gave the (1*R**,2*R**,3*S**,5*R**,6*R**)-cycloadduct **12d** in 25% yield. On the other hand, treatment of *ortho*-disubstituted azomethine imide **6e** with **7** gave a mixture of diastereomeric cycloadducts **11e** and **12e** in a ratio of 66:34. Upon chromatographic separation, isomeric cycloadducts **11e** and **12e** were isolated in 19 and 10% yields, respectively. *ortho*-Disubstituted 5-(1*H*-indol-3-yl) dipoles **6i**, **6j** did not react with **7** in refluxing anisole (Scheme 2, Table II).



SCHEME 2

Both cycloadditions of *ortho*-disubstituted dipoles **6d** and **6e** to dimethyl fumarate (**8**) were selective furnishing dimethyl (1*R**,2*R**,3*S**,5*R**,6*R**)-6-benzamido-3,5-diaryl-7-oxohexahydropyrazolo[1,2-*a*]pyrazole-1,2-dicarboxylates **12d** and **12e** in 34 and 54% yields, respectively. However, the reaction of 5-(1*H*-indol-3-yl) substituted dipole **6j** with **8** was not selective

and gave a mixture of diastereomers **12j** and **13j** in a ratio of 44:56. Subsequent chromatographic separation afforded isomerically pure cycloadducts **12j** and **13j** in 14 and 18% yields, respectively (Scheme 3, Table II).

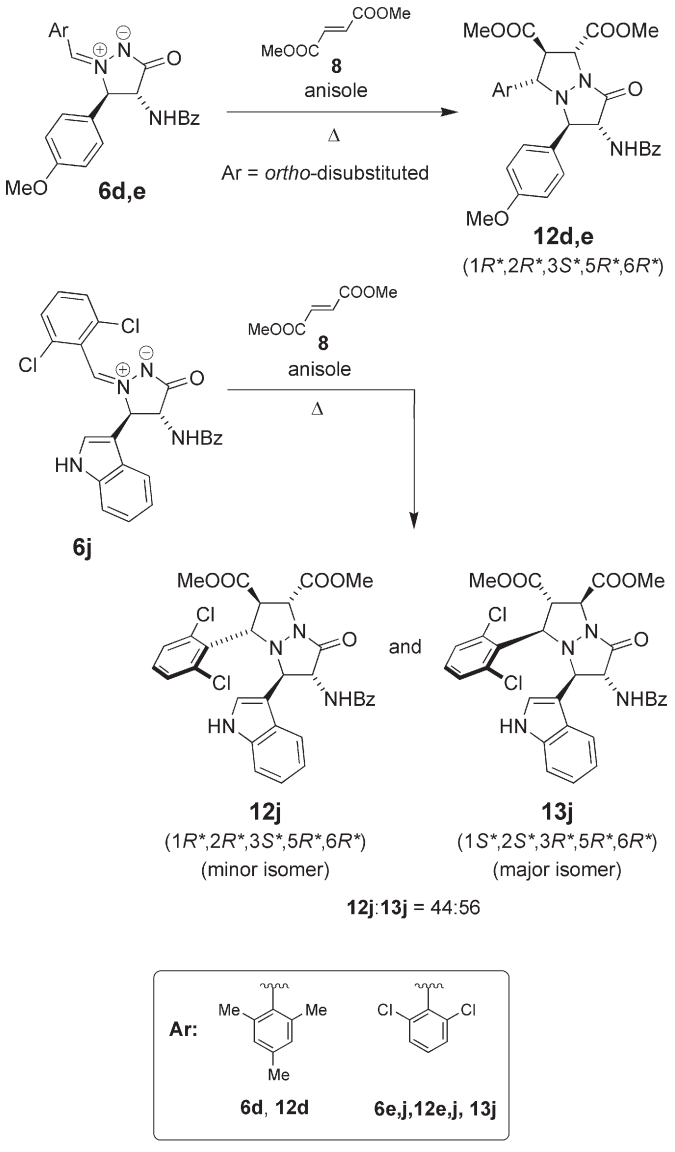
Finally, cycloadditions of *ortho*-unsubstituted dipoles **6a**–**6c**, **6g** to methyl acrylate (**9**) were carried out. Azomethine imides **6b**, **6c**, **6g** reacted selectively to give (1*R**,3*R**,5*R**,6*R**)-3-aryl-6-benzamido-5-(4-methoxyphenyl)-7-oxohexahydropyrazolo-[1,2-*a*]pyrazole-1-carboxylates **14b**, **14c**, and **14g** in 64–65% yields. On the other hand, 1′-benzylidene-substituted azomethine imide **6a** gave a mixture of diastereomers **14a** and **15a** in a ratio of 86:14. Upon chromatographic separation, isomerically pure compounds **14a** and **15a** were isolated in 37 and 7% yields, respectively (Scheme 4, Table II).

Formation of cycloadducts **12d** and **12e** with *trans*-configuration around the C(1)–C(2) bond in cycloadditions of *ortho*-disubstituted dipoles **6d**, **6e** to the *cis*-dipolarophile **7** was surprising, yet explainable. At first glance, a long reaction time (15–17 h, cf. Table II) seems an obvious explanation, since it allows a thermal *cis*→*trans* epimerisation at C(1) in the primary

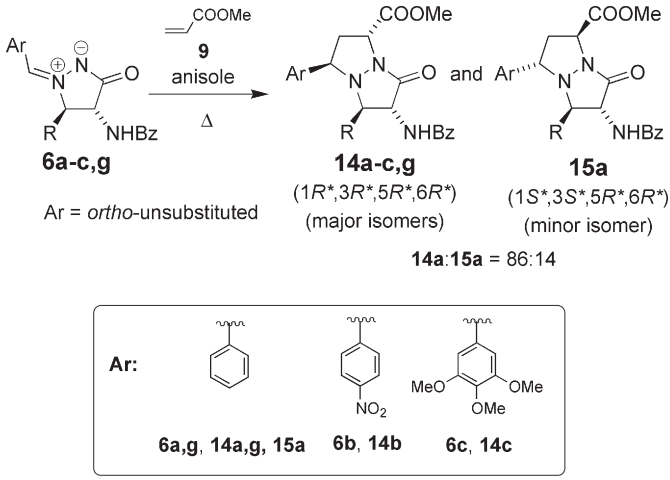
TABLE II
Selected experimental data for cycloadducts **10**–**15**[a]

Compound	R	Ar	Time, h	Yield, %
10a	4-methoxyphenyl	Ph	10	27
10b	4-methoxyphenyl	4-nitrophenyl	13	37
10c	4-methoxyphenyl	3,4,5-trimethoxyphenyl	18	21
10g	1*H*-indol-3-yl	Ph	14	69
11e	4-methoxyphenyl	2,6-dichlorophenyl	17	19
12d	4-methoxyphenyl	2,4,6-trimethylphenyl	15[b], 7[c]	25[b], 34[c]
12e	4-methoxyphenyl	2,6-dichlorophenyl	17[b], 5[c]	10[b], 54[c]
12j	1*H*-indol-3-yl	2,6-dichlorophenyl	11	14
13j	1*H*-indol-3-yl	2,6-dichlorophenyl	11	18
14a	4-methoxyphenyl	Ph	10	37
14b	4-methoxyphenyl	4-nitrophenyl	11	65
14c	4-methoxyphenyl	3,4,5-trimethoxyphenyl	11	65
14g	1*H*-indol-3-yl	Ph	8	64
15a	4-methoxyphenyl	Ph	10	7

[a] All reactions were carried out in refluxing anisole. [b] Isolated upon reaction with dimethyl maleate (**7**). [c] Isolated upon reaction with dimethyl fumarate (**8**).


Ar
NHBz
MeO
6d,e
COOMe
MeOOC
8
anisole
Δ
Ar = ortho-disubstituted
MeOOC
COOMe
Ar
NHBz
MeO
12d,e
(1R*,2R*,3S*,5R*,6R*)
Cl
Cl
NHBz
HN
6j
COOMe
MeOOC
8
anisole
Δ
MeOOC
COOMe
Cl
Cl
NHBz
HN
12j
(1R*,2R*,3S*,5R*,6R*)
(minor isomer)
and
MeOOC
COOMe
Cl
Cl
NHBz
HN
13j
(1S*,2S*,3R*,5R*,6R*)
(major isomer)
12j:13j = 44:56
Ar:
Me
Me
Me
6d, 12d
Cl
Cl
6e,j,12e,j, 13j

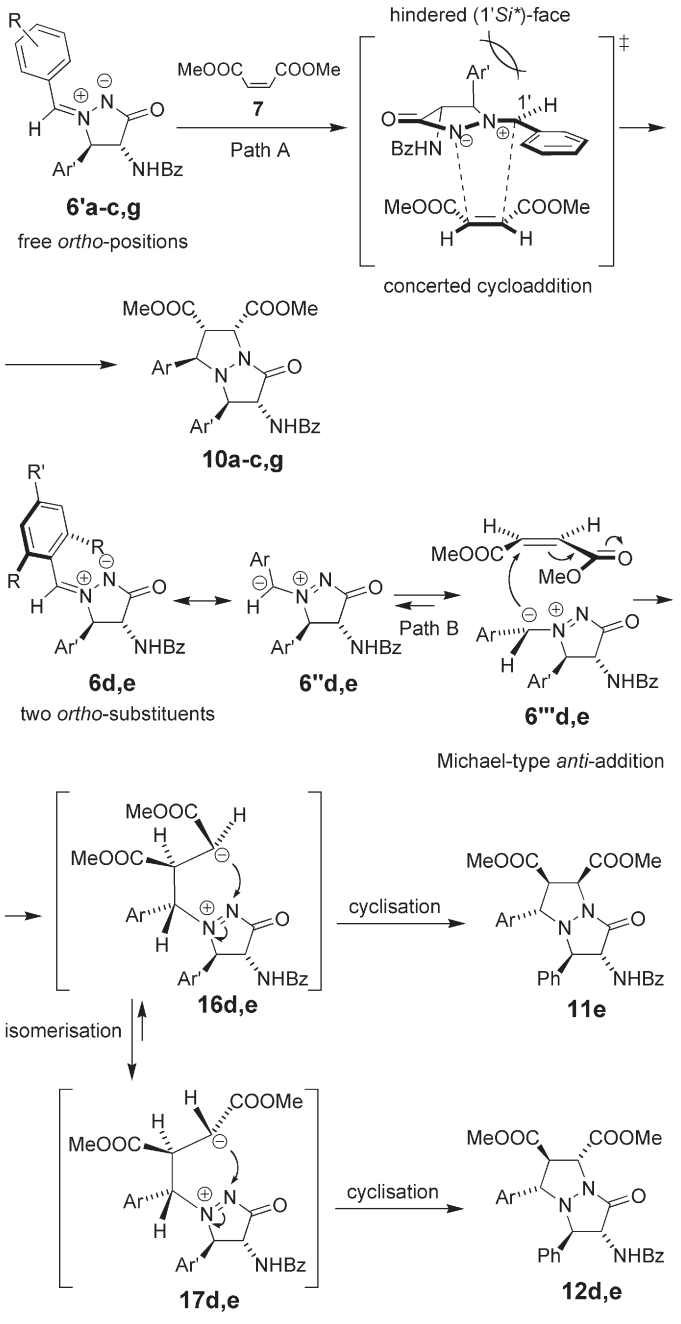
SCHEME 3



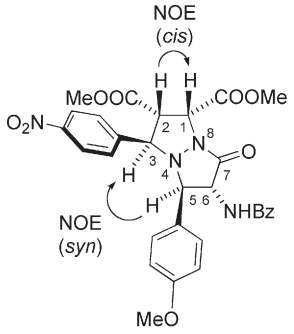
SCHEME 4

cycloadducts **11** and thermal *Z*→*E* isomerisation of maleate **7** into fumarate **8** as well. In both cases, 1,2-*trans* cycloadducts **12** would be formed. However, epimerisation at C(1) was not observed in the reactions of *ortho*-unsubstituted dipoles **6a**–**6c**, **6g** with dimethyl maleate (**7**), even though the reaction time was essentially the same (10–18 h). On the other hand, involvement of different cycloaddition mechanisms[10,11] with respect to the *ortho*-substituents in dipoles **6** offers another possible explanation. Accordingly, reactions of *ortho*-unsubstituted dipoles **6a**–**6c**, **6g** could be explained by the concerted 1,3-dipolar cycloaddition mechanism via the *endo*-approach of dipolarophile **7** from the less hindered (1′*Re*)-face of the planar conformer of the dipole **6′** (Scheme 5, Path A)[10,11,14]. On the other hand, *ortho*-disubstituted dipoles **6d**, **6e** cannot adopt a planar conformation **6′** and they can react by a two-step mechanism via Michael-type addition of **7** to the conformer **6″** to give the zwitterion (or a diradical[21]) **16**. Subsequent cyclisation of **16** would lead to the (1*S**,2*R**,3*S**,5*R**,6*R**)-isomer **11**, whilst fast isomerisation of the intermediate **16** into the thermodynamically more stable *trans*-isomer **16′** followed by cyclisation would then give the (1*R**,2*R**,3*S**,5*R**,6*R**)-cycloadduct **12** (Scheme 5, Path B).

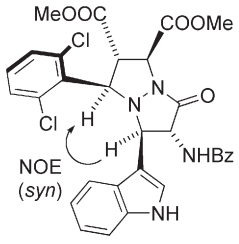
The structures of novel compounds **2b**, **6a**–**6j**, **10a**–**10c**, **10g**, **11e**, **12d**, **12e**, **12j**, **13j**, **14a**–**14c**, **14g**, and **15a** were determined by spectroscopic methods (NMR, IR, MS) and by elemental analyses for C, H, and N. Compounds **6g**–**6j**, **10b**, **12j**, **14c**, and **15a** were not obtained in analytically


R
MeOOC
COOMe
7
Path A
hindered (1'Si*)-face
Ar'
1'
H
BzHN
MeOOC
COOMe
H
H
‡
concerted cycloaddition
6'a-c,g
free ortho-positions
Ar'
NHBz
10a-c,g
R'
R
6d,e
two ortho-substituents
6''d,e
Path B
MeO
6'''d,e
Michael-type anti-addition
16d,e
cyclisation
11e
Ph
isomerisation
17d,e
12d,e

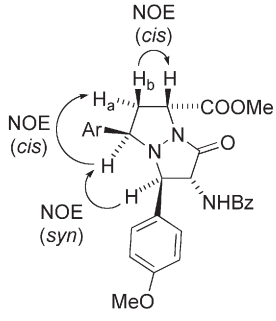
SCHEME 5



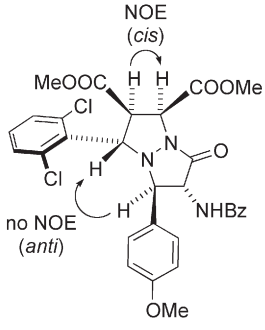
Compound **10b**



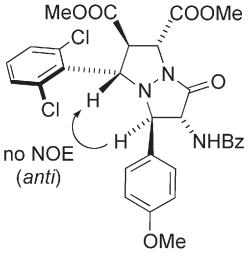
Compound **13j**



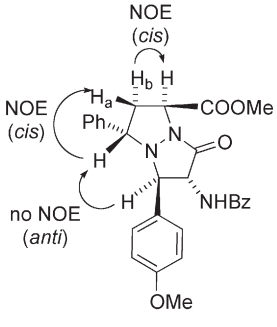
Compound **14c**
(Ar = 3,4,5-trimethoxyphenyl)



Compound **11e**



Compound **12e**



Compound **15a**

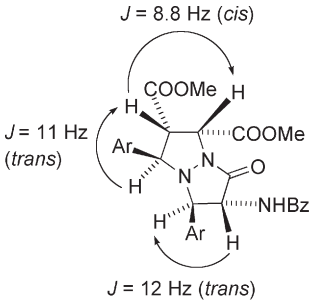
FIG. 2
Selected crucial NOE interactions

pure form. Their identities were confirmed by ^{13}C NMR and HRMS. The relative configurations of cycloadducts **10**–**15** were determined by correlation of proton chemical shifts (δ_H) and vicinal coupling constants ($^3J_{H-H}$) as well as by NOESY spectroscopy. NOE between H-3 and H-5 in compounds **10b**, **13j**, and **14c** was in agreement with the *syn*-orientation, whilst the absence of NOE supported the *anti*-orientation between H-3 and H-5 in compounds **11e**, **12e**, and **15a**. Similarly, the *cis*-configuration around the C(1)–C(2) in compounds **10b**, **11e**, and **14c** was confirmed by NOE between H-1 and H-2. Finally, the (1*R**)-configuration in cycloadduct **14c** and (1*S**)-configuration in cycloadduct **15a** were confirmed by NOE between H-1 and Hb-2 and between Ha-2 and H3 (Fig. 2). Finally, the ^1H NMR data of cycloadducts **10**–**15** were in agreement with typical literature values for closely related compounds, for example: *J*(1,2) = 8–9 Hz (*cis*) and 1–7 Hz (*trans*), *J*(2,3) = 6 Hz (*cis*) and 9–11 Hz (*trans*), and *J*(5,6) = 8.5–12 Hz (*trans*) (Fig. 3, Table III)[10–14].

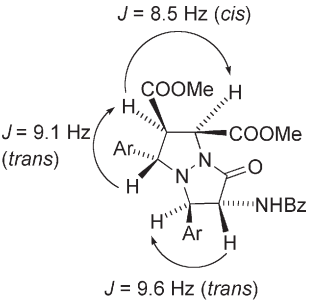
TABLE III
Selected NMR data for cycloadducts **10**–**15**

Compd.	δ, ppm					$^3J_{H-H}$, Hz			
	1-H	2-H	3-H	5-H	6-H	1-2	2-3	5-6	1-3
10a	4.81	3.82	4.55	4.27	5.58	8.8	10.9	12.1	0.8
10b	4.84	3.78	4.50	4.31	5.60	8.7	11.0	12.1	0.8
10c	4.79	3.77	4.30	4.26	5.65	8.8	11.0	12.2	0.8
10g	4.84	3.80	4.42	4.72	5.80	8.9	11.0	12.2	0.8
11e	5.75	4.74	5.25	4.25	5.19	8.5	9.1	9.6	–
12d	5.12	3.84	4.27	4.79	5.68	5.2	9.3	8.6	–
12e	5.29	4.18	4.65	4.98	5.94	4.9	9.1	11.7	–
12j	5.37	4.24	4.75	5.21	6.01	4.5	9.2	11.7	–
13j	5.42	4.45	5.12	4.85	5.92	4.5	9.0	8.7	–

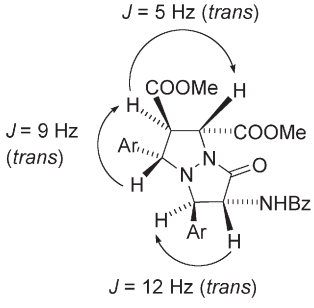
	δ, ppm						$^3J_{H-H}$, Hz				
	1-H	2-Ha	2-Hb	3-H	5-H	6-H	1-2a	1-2b	2a-3	2b-3	5-6
14a	4.57	2.58	2.78	4.05	4.20	5.54	1.1	9.4	5.5	11.5	12.1
14b	4.59	2.64	2.72	4.20	4.22	5.57	1.0	8.7	5.7	11.2	12.0
14c	4.54	2.57	2.72	4.01	4.18	5.58	0.7	9.0	5.4	11.3	12.0
14g	4.59	2.60	2.76	4.13	4.63	5.75	1.1	9.1	5.7	11.3	12.1
15a	4.70	2.40	2.95	3.68	4.80	5.60	6.6	9.8	9.1	7.4	8.5



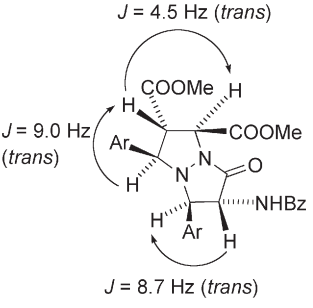
Compounds **10a-c,g**



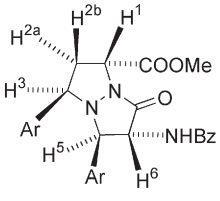
Compound **11e**



Compounds **12d,e,j**

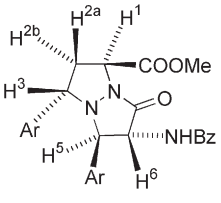


Compound **13j**



$J_{1\text{-}2a}$ = 1 Hz (*trans*)
$J_{1\text{-}2b}$ = 9 Hz (*cis*)
$J_{2a\text{-}3}$ = 6 Hz (*cis*)
$J_{2b\text{-}3}$ = 11 Hz (*trans*)
$J_{5\text{-}6}$ = 12 Hz (*trans*)

Compounds **14a-c,g**



$J_{1\text{-}2a}$ = 7 Hz (*trans*)
$J_{1\text{-}2b}$ = 10 Hz (*cis*)
$J_{2a\text{-}3}$ = 9 Hz (*cis*)
$J_{2b\text{-}3}$ = 7 Hz (*trans*)
$J_{5\text{-}6}$ = 8.5 Hz (*trans*)

Compound **15a**

FIG. 3
Selected crucial NMR interaction constants

CONCLUSIONS

Cycloadditions of azomethine imides **6a**–**6e**, **6g**, **6j** to olefinic dipolarophiles **7**–**9** furnished novel polysubstituted pyrazolo[1,2-*a*]pyrazolidinones **10**–**15** as heterocyclic dipeptides with *O*-methyltyrosine and tryptophan as the N-terminal amino acids. The title reactions followed the same regiocontrol and stereocontrol as established previously for reactions of their closely related 5-phenyl analogues[10–12]. However, 5-(4-methoxyphenyl)-substituted dipoles **6a**–**6e** and dipoles **6g**, **6j** with indolyl group at position 5 were less reactive. This was reflected in longer reaction times and moderate yields of cycloadducts **10**–**15** and, in some cases, also in lower stereoselectivity. The results of this study offer further evidence that general stereochemical pattern[10–12] in cycloadditions of 4-(acylamino)-5-(arylmethylidene)-3-oxopyrazolidin-1-ium-2-ides is dependent on (i) stereodirecting group at position 5, (ii) *ortho*-substituents at the 1′-Ar residue, and (iii) type of the dipolarophile. In conclusion, 1,3-dipolar cycloadditions of 5-substituted 4-(acylamino)pyrazolidin-3-one derived azomethine imides offer an easy access to pyrazolo[1,2-*a*]pyrazole-based heterocyclic dipeptides with variable amino acid sequence and variable, yet predictable stereochemistry.

EXPERIMENTAL

Melting points were determined on a Kofler micro hot stage. The NMR spectra (δ, ppm; *J*, Hz) were obtained on a Bruker Avance DPX 300 at 300 MHz for ^{1}H and 75.5 MHz for ^{13}C, using DMSO-d_6 and $CDCl_3$ with TMS as the internal standard, as solvents. Mass spectra were recorded on an AutoSpecQ and a Q-TOF Premier spectrometer, IR spectra (ν, cm^{-1}) on a Perkin–Elmer Spectrum BX FTIR spectrophotometer. Microanalyses were performed on a Perkin–Elmer CHN Analyser 2400 II. Flash chromatography (FC) was performed on silica gel (Fluka, silica gel 60, 0.04–0.06 mm). The isomer ratios were determined by ^{1}H NMR.

Aromatic aldehydes **5a**–**5f**, dimethyl maleate (**7**), dimethyl fumarate (**8**), and methyl acrylate (**9**) are commercially available (Sigma Aldrich). (1*Z*,4*R**,5*R**)-4-benzamido-5-(4-methoxyphenyl)pyrazolidin-3-one (**2a**)[18] and methyl 2-benzamido-3-(1*H*-indol-3-yl)propenoate (**4**)[19] were prepared according to the literature procedures.

(4*R**,5*R**)-4-Benzamido-5-(1*H*-indol-3-yl)pyrazolidin-3-one (**2b**)

A mixture of methyl 2-benzamido-3-(1*H*-indol-3-yl)propenoate (**4**)[19] (9.610 g, 30 mmol), hydrazine hydrate (100%, 4.5 ml, 90 mmol), ethanol (20 ml), and water (18 ml) was heated under reflux for 6 h. The reaction mixture was cooled, the precipitate was collected by filtration, and recrystallised from ethanol to give **2b**. Yield: 6.78 g (71%) of a white solid. M.p. 227–232 °C (EtOH). IR (KBr): 3299, 1705 (C=O), 1662 (C=O), 1580, 1522. ^{1}H NMR (300 MHz, DMSO-d_6): 4.82, d, 1 H, *J*(4,5) = 11.7 (H-5); 5.18, dd, 1 H, *J*(4,5) = 11.7, *J*(4,NH) = 9.4 (H-4); 5.20, s, 1 H (H-1); 7.08–7.14, m, 2 H (2 H of Ar); 7.35–7.60, m, 6 H (6 H of Ar); 7.84–7.89,

m, 2 H (2 H of Ar); 8.83, d, 1 H, *J*(4,NH) = 9.4 (N**H**COPh); 9.51, s, 1 H (H-2); 11.05, s, 1 H (H-1′). For $C_{18}H_{16}N_4O_2$ (320.35) calculated: C 67.49%, H 5.03%, N 17.49%; found: C 67.21%, H 5.11%, N 17.32%.

Preparation of (1*Z*,4*R**,5*R**)-5-Aryl-1-(arylmethylidene)-4-benzamido-3-oxopyrazolidin-1-ium-2-ides **6a**–**6j**. General Procedure

A mixture of pyrazolidinone **2** (3 mmol), aromatic aldehyde **5** (5 mmol), and anhydrous ethanol (9 ml) was heated under reflux for 10 min. Then, trifluoroacetic acid (6 drops) was added through a reflux condenser and the mixture was heated under reflux for 2 h. The reaction mixture was cooled to 0 °C (ice bath), the precipitate was collected by filtration and washed with diethyl ether (5 ml) to give **6**. The following compounds were prepared in this manner.

(1Z,4R,5R*)-4-Benzamido-1-benzylidene-5-(4-methoxyphenyl)-3-oxopyrazolidin-1-ium-2-ide* (**6a**). This compound was prepared from **2a** (934 mg, 3 mmol) and benzaldehyde (**5a**; 0.531 mg, 5 mmol). Yield: 1.089 g (91%) of a white solid. M.p. 220–222 °C. IR (KBr): 3447, 1666 (C=O), 1652 (C=O), 1589, 1514, 1487. ^{1}H NMR (300 MHz, DMSO-d_6): 3.78, s, 3 H (OMe); 4.71, dd, 1 H, *J*(4,5) = 5.1, *J*(4,NH) = 7.9 (H-4); 5.72, d, 1 H, *J*(4,5) = 5.1 (H-5); 7.00–7.05, m, 2 H (2 H of Ar); 7.30, s, 1 H (H-1′); 7.41–7.57, m, 8 H (8 H of Ar); 7.86–7.90, m, 2 H (2 H of Ar); 8.31–8.36, m, 2 H (2 H of Ar); 9.17, d, 1 H, *J*(4,NH) = 7.9 (NH). For $C_{24}H_{21}N_3O_3$ (399.44) calculated: C 72.16%, H 5.30%, N 10.52%; found: C 71.97%, H 5.48%, N 10.49%.

(1Z,4R,5R*)-4-Benzamido-5-(4-methoxyphenyl)-1-(4-nitrobenzylidene)-3-oxo-pyrazolidin-1-ium-2-ide* (**6b**). This compound was prepared from **2a** (934 mg, 3 mmol) and 4-nitrobenzaldehyde (**5b**; 756 mg, 5 mmol). Yield: 1.292 g (97%) of a yellowish solid. M.p. 162–166 °C. IR (KBr): 3447, 1678 (C=O), 1668 (C=O), 1602, 1576, 1517. ^{1}H NMR (300 MHz, DMSO-d_6): 3.78, s, 3 H (OMe); 4.74, dd, 1 H, *J*(4,5) = 5.3, *J*(4,NH) = 7.9 (H-4); 5.82, d, 1 H, *J*(4,5) = 5.3 (H-5); 7.01–7.07, m, 2 H (2 H of Ar); 7.43, s, 1 H (H-1′); 7.45–7.60, m, 5 H (5 H of Ar); 7.85–7.91, m, 2 H (2 H of Ar); 8.33–8.39, m, 2 H (2 H of Ar); 8.56–8.62, m, 2 H (2 H of Ar); 9.17, d, 1 H, *J*(4,NH) = 7.9 (NH). For $C_{24}H_{20}N_4O_5$ (444.44) calculated: C 64.86%, H 4.54%, N 12.61%; found: C 64.65%, H 4.60%, N 12.55%.

(1Z,4R,5R*)-4-Benzamido-5-(4-methoxyphenyl)-3-oxo-1-(3,4,5-trimethoxybenzylidene)pyrazolidin-1-ium-2-ide* (**6c**). This compound was prepared from **2a** (934 mg, 3 mmol) and 3,4,5-trimethoxybenzaldehyde (**5c**; 981 mg, 5 mmol). Yield: 1.218 g (83%) of a white solid. M.p. 224–226 °C. IR (KBr): 3258, 1664 (C=O), 1643 (C=O), 1596, 1542. ^{1}H NMR (300 MHz, DMSO-d_6): 3.76, s, 6 H (2 × OMe); 3.78, s, 3 H (OMe); 3.81, s, 3 H (OMe); 4.68, dd, 1 H, *J*(4,5) = 5.7, *J*(4,NH) = 7.9 (H-4); 5.68, dd, 1 H, *J*(1′,5) = 0.7, *J*(4,5) = 5.7 (H-5); 6.99–7.04, m, 2 H (2 H of Ar); 7.24, s, 1 H (H-1′); 7.40–7.59, m, 5 H (5 H of Ar); 7.78–7.84, m, 2 H (2 H of Ar); 7.83–7.89, m, 2 H (2 H of Ar); 9.15, d, 1 H, *J*(4,NH) = 7.9 (NH). For $C_{27}H_{27}N_3O_6$ (489.52) calculated: C 66.25%, H 5.56%, N 8.58%; found: C 65.99%, H 5.71%, N 8.47%.

(1Z,4R,5R*)-4-Benzamido-5-(4-methoxyphenyl)-3-oxo-1-(2,4,6-trimethylbenzylidene)pyrazolidin-1-ium-2-ide* (**6d**). This compound was prepared from **2a** (934 mg, 3 mmol) and 2,4,6-trimethylbenzaldehyde (**5d**; 725 mg, 5 mmol). Yield: 1.124 g (85%) of a white solid. M.p. 257–259 °C. IR (KBr): 3327, 1676 (C=O), 1652 (C=O), 1597, 1541. ^{1}H NMR (300 MHz, DMSO-d_6): 2.13, s, 6 H (2 × **Me**Ar); 2.26, s, 3 H (**Me**Ar); 3.79, s, 3 H (OMe); 4.74, dd, 1 H, *J*(4,5) = 6.2, *J*(4,NH) = 7.9 (H-4); 5.72, dd, 1 H, *J*(1′,5) = 1.3, *J*(4,5) = 6.2 (H-5); 6.90, s, 2 H (C_6H_4); 7.03–7.09, m, 2 H (2 H of Ar); 7.44, s, 1 H (H-1′); 7.45–7.60, m, 5 H (5 H of Ar);

7.85–7.90, m, 2 H (2 H of Ar); 9.14, d, 1 H, *J*(4,NH) = 7.9 (NH). For $C_{27}H_{27}N_3O_3$ (441.52) calculated: C 73.45%, H 6.16%, N 9.52%; found: C 73.46%, H 6.30%, N 9.65%.

(1Z,4R,5R*)-4-Benzamido-1-(2,6-dichlorobenzylidene)-5-(4-methoxyphenyl)-3-oxopyrazolidin-1-ium-2-ide* (**6e**). This compound was prepared from **2a** (934 mg, 3 mmol) and 2,6-dichlorobenzaldehyde (**5e**; 875 mg, 5 mmol). Yield: 1.333 g (95%) of a white solid. M.p. 222–223 °C. IR (KBr): 3251, 1673 (C=O), 1645 (C=O), 1597, 1578, 1516. ^{1}H NMR (300 MHz, DMSO-d_6): 3.79, s, 3 H (OMe); 4.85, dd, 1 H, *J*(4,5) = 6.9, *J*(4,NH) = 7.9 (H-4); 5.72, dd, 1 H, *J*(1′,5) = 1.6, *J*(4,5) = 6.9 (H-5); 7.03–7.10, m, 2 H (2 H of Ar); 7.35, s, 1 H (H-1′); 7.45–7.60, m, 8 H (8 H of Ar); 7.84–7.91, m, 2 H (2 H of Ar); 9.14, d, 1 H, *J*(4,NH) = 7.9 (NH). For $C_{24}H_{19}Cl_2N_3O_3$ (468.33) calculated: C 61.55%, H 4.09%, N 8.97%; found: C 61.55%, H 4.18%, N 8.81%.

(1Z,4R,5R*)-4-Benzamido-1-(2,4-dichlorobenzylidene)-5-(4-methoxyphenyl)-3-oxopyrazolidin-1-ium-2-ide* (**6f**). This compound was prepared from **2a** (934 mg, 3 mmol) and 2,6-dichlorobenzaldehyde (**5f**; 875 mg, 5 mmol). Yield: 1.359 g (97%) of a white solid. M.p. 206–208 °C. IR (KBr): 3353, 3312, 1673 (C=O), 1662 (C=O), 1589. ^{1}H NMR (300 MHz, DMSO-d_6): 3.78, s, 3 H (OMe); 4.79, dd, 1 H, *J*(4,5) = 5.9, *J*(4,NH) = 7.8 (H-4); 5.92, dd, 1 H, *J*(1′,5) = 1.3, *J*(4,5) = 5.9 (H-5); 7.00–7.08, m, 2 H (2 H of Ar); 7.37, s, 1 H (H-1′); 7.46–7.60, m, 5 H (5 H of Ar); 7.66–7.74, m, 1 H (1 H of Ar); 7.80, d, 1 H, *J* = 2.1 (1 H of Ar); 7.85–7.89, m, 2 H (2 H of Ar); 9.18–2.24, m, 2 H (1 H of Ar, NH). For $C_{24}H_{19}Cl_2N_3O_3$ (468.33) calculated: C 61.55%, H 4.09%, N 8.97%; found: C 61.64%, H 4.23%, N 8.89%.

(1Z,4R,5R*)-4-Benzamido-1-benzylidene-5-(1H-indol-3-yl)-3-oxopyrazolidin-1-ium-2-ide* (**6g**). This compound was prepared from **2b** (961 mg, 3 mmol) and benzaldehyde (**5a**; 0.531 mg, 5 mmol). Yield: 945 mg (77%) of a white solid. M.p. 236–238 °C. IR (KBr): 3265, 3190, 1663 (C=O), 1638 (C=O), 1593, 1545. EIMS, *m/z*: 408 (M^+). ^{1}H NMR (300 MHz, DMSO-d_6): 5.02, dd, 1 H, *J*(4,5) = 6.7, *J*(4,NH) = 8.2 (H-4); 5.98, d, 1 H, *J*(1′,5) = 1.2, *J*(4,5) = 6.7 (H-5); 7.01–7.07, m, 1 H (1 H of Ar); 7.14–7.18, m, 1 H (1 H of Ar); 7.29–7.35, m, 2 H (2 H of Ar); 7.43–7.58, m, 8 H (H-1′, 7 H of Ar); 7.76, d, 1 H, *J* = 2.4 (H-2″); 8.30–8.34, m, 2 H (2 H of Ar); 9.14, d, 1 H, *J*(4,NH) = 8.2 (NH); 9.13–9.17, m, 1 H (1 H of Ar); 11.43, d, 1 H, *J* = 2.4 (H-1″). ^{13}C NMR (75.5 MHz, DMSO-d_6): 57.1, 72.1, 110.1, 113.4, 118.5, 120.8, 122.9, 124.7, 126.8, 128.1, 128.7, 129.3, 129.6, 130.3, 132.1, 132.5, 133.4, 134.4, 137.9, 166.8, 180.7. For $C_{25}H_{20}N_4O_2$ (408.45) calculated: C 73.51%, H 4.94%, N 13.72%; found: C 73.26%, H 5.03%, N 12.59%. HRMS, *m/z*: calculated for $C_{25}H_{20}N_4O_2$ (M^+) 408.1586, found 408.1599.

(1Z,4R,5R*)-4-Benzamido-5-(1H-indol-3-yl)-1-(4-nitrobenzylidene)-3-oxopyrazolidin-1-ium-2-ide* (**6h**). This compound was prepared from **2b** (961 mg, 3 mmol) and 4-nitrobenzaldehyde (**5b**; 0.756 ml, 5 mmol). Yield: 561 mg (41%) of a yellowish solid. M.p. 218–221 °C. IR (KBr): 3416, 3278, 1663 (C=O), 1601, 1579, 1518. EIMS, *m/z*: 454 (MH^+). ^{1}H NMR (300 MHz, DMSO-d_6): 5.00, dd, 1 H, *J*(4,5) = 6.7, *J*(4,NH) = 8.0 (H-4); 6.09, d, 1 H, *J*(1′,5) = 1.2, *J*(4,5) = 6.7 (H-5); 7.01–7.08, m, 1 H (1 H of Ar); 7.15–7.19, m, 1 H (1 H of Ar); 7.29–7.33, d, 1 H, *J* = 7.9 (1 H of Ar); 7.46–7.52, m, 4 H (H-1′, 3 H of Ar); 7.53–7.59, m, 1 H (1 H of Ar); 7.80, d, 1 H, *J* = 2.5 (H-2″); 7.86, m, 2 H (2 H of Ar); 8.33, m, 2 H (2 H of Ar); 8.58, m, 2 H (2 H of Ar); 9.18, d, 1 H, *J*(4,NH) = 8.1 (NH); 11.48, d, 1 H, *J* = 2.5 (H-1″). For $C_{25}H_{19}N_5O_4$ (453.45) calculated: C 66.22%, H 4.22%, N 15.44%; found: C 66.18%, H 4.40%, N 14.36%. HRMS, *m/z*: calculated for $C_{25}H_{20}N_5O_4$ (MH^+) 454.1515, found 454.1507.

(1Z,4R,5R*)-4-Benzamido-5-(1H-indol-3-yl)-3-oxo-1-(2,4,6-trimethylbenzylidene)pyrazolidin-1-ium-2-ide* (**6i**). This compound was prepared from **2b** (961 mg, 3 mmol) and 2,4,6-trimethylbenzaldehyde (**5d**; 725 mg, 5 mmol). Yield: 951 mg (70%) of a white solid. M.p. 245–247 °C. IR (KBr): 3269, 1669 (C=O), 1645 (C=O), 1597, 1550. EIMS, *m/z*: 451 (MH^+).

^{1}H NMR (300 MHz, DMSO-d_6): 1.98, s, 6 H (2 × **Me**Ar); 2.25, s, 3 H (**Me**Ar); 5.10, dd, 1 H, *J*(4,5) = 7.1, *J*(4,NH) = 8.1 (H-4); 5.99, d, 1 H, *J*(1′,5) = 1.5, *J*(4,5) = 7.1 (H-5); 6.86, s, 2 H (C_6H_2); 7.08–7.12, m, 2 H (2 H of Ar); 7.17–7.21, m, 1 H (1 H of Ar); 7.38–7.43, m, 1 H (1 H of Ar); 7.45–7.55, m, 5 H (H-1′, 4 H of Ar); 7.79, d, 1 H, *J* = 2.4 (H-2″); 7.83–7.89, m, 2 H (2 H of Ar); 9.11, d, 1 H, *J*(4,NH) = 8.1 (NH); 11.43, d, 1 H, *J* = 2.4 (H-1″). ^{13}C NMR (75.5 MHz, DMSO-d_6): 19.2, 20.6, 56.5, 69.9, 108.9, 112.4, 112.7, 117.9, 119.6, 122.0, 123.7, 126.3, 127.1, 127.8, 128.2, 131.4, 132.4, 133.4, 136.4, 137.0, 139.1, 165.9, 179.1. HRMS, *m/z*: calculated for $C_{28}H_{27}N_4O_2$ (MH^+) 451.2134, found 451.2145.

(1Z,4R,5R*)-4-Benzamido-1-(2,6-dichlorobenzylidene)-5-(1H-indol-3-yl)-3-oxopyrazolidin-1-ium-2-ide* (**6j**). This compound was prepared from **2b** (961 mg, 3 mmol) and 2,6-dichlorobenzaldehyde (**5e**; 875 mg, 5 mmol). Yield: 1.170 g (82%) of a white solid. M.p. 226–228 °C. IR (KBr): 3215, 3178, 1680 (C=O), 1652 (C=O), 1593, 1544. EIMS, *m/z*: 476 (M^+). ^{1}H NMR (300 MHz, DMSO-d_6): 5.24, dd, 1 H, *J*(4,5) = 7.1, *J*(4,NH) = 8.2 (H-4); 6.05, d, 1 H, *J*(1′,5) = 1.7, *J*(4,5) = 7.1 (H-5); 7.09–7.12, m, 2 H (2 H of Ar); 7.18–7.22, m, 1 H (1 H of Ar); 7.36–7.40, m, 1 H (1 H of Ar); 7.46–7.60, m, 7 H (H-1′, 6 H of Ar); 7.81–7.89, m, 3 H (3 H of Ar); 9.11, d, 1 H, *J*(4,NH) = 8.2 (NH); 11.47, d, 1 H, *J* = 2.1 (H-1″). ^{13}C NMR (75.5 MHz, DMSO-d_6): 19.1, 33.3, 70.6, 75.3, 81.5, 82.6, 85.1, 86.9, 90.1, 91.2, 91.3, 91.7, 91.8, 94.6, 95.2, 96.2, 96.3, 96.4, 100.1, 128.9, 142.3. HRMS, *m/z*: calculated for $C_{25}H_{18}Cl_2N_4O_2$ (M^+) 476.0807, found 476.0819.

Preparation of Cycloadducts **10**–**15**. General Procedures

Procedure A. A mixture of azomethine imide **6** (1 mmol), dipolarophile **7**–**9** (2 mmol), and anisole (5 ml) was heated under reflux for 5–18 h. Volatile components were evaporated in vacuo and the residue was triturated with diethyl ether (5 ml). The precipitate was collected by filtration and washed with diethyl ether (5 ml) to give cycloadduct **10**–**15**.

Procedure B. A mixture of azomethine imide **6** (1 mmol), dipolarophile **7**–**9** (2 mmol), and anisole (5 ml) was heated under reflux for 7–17 h. Volatile components were evaporated in vacuo and the residue was purified by column chromatography (CC) on silica gel. Fractions containing the corresponding cycloadducts were combined and evaporated in vacuo to give cycloadducts **10**–**15**.

The following compounds were prepared in this manner.

Dimethyl (1R,2S*,3R*,5R*,6R*)-6-benzamido-5-(4-methoxyphenyl)-7-oxo-3-phenylhexahydropyrazolo[1,2-a]pyrazole-1,2-dicarboxylate* (**10a**). Prepared from dipole **6a** (399 mg, 1 mmol) and dimethyl maleate (**7**; 287 mg, 2 mmol), procedure *A*, reflux for 10 h. Yield: 145 mg (27%) of a white solid. M.p. 185–186 °C. IR (KBr): 3360, 1744 (C=O), 1708 (C=O), 1666 (C=O), 1612. ^{1}H NMR (300 MHz, $CDCl_3$): 3.57, s, 3 H (OMe); 3.62, s, 3 H (OMe); 3.82, dd, 1 H, *J*(1,2) = 8.8, *J*(2,3) = 10.9 (H-2); 3.86, s, 3 H (OMe); 4.27, d, 1 H, *J*(5,6) = 12.1 (H-5); 4.55, d, 1 H, *J*(2,3) = 10.9 (H-3); 4.81, dd, 1 H, *J*(1,2) = 8.8, *J*(1,3) = 0.8 (H-1); 5.58, dd, 1 H, *J*(5,6) = 12.1, *J*(6,NH) = 8.3 (H-6); 6.48–6.54, m, 2 H (2 H of Ar); 6.59, d, 1 H, *J*(6,NH) = 8.3 (NH); 7.00–7.05, m, 3 H (3 H of Ar); 7.07–7.16, m, 4 H (4 H of Ar); 7.33–7.40, m, 2 H (2 H of Ar); 7.42–7.50, m, 1 H (1 H of Ar); 7.68–7.74, m, 2 H (2 H of Ar). For $C_{30}H_{29}N_3O_7$ (543.57) calculated: C 66.29%, H 5.38%, N 7.73%; found: C 66.21%, H 5.50%, N 7.70%.

Dimethyl (1R,2S*,3R*,5R*,6R*)-6-benzamido-5-(4-methoxyphenyl)-3-(4-nitrophenyl)-7-oxohexahydropyrazolo[1,2-a]pyrazole-1,2-dicarboxylate* (**10b**). Prepared from dipole **6b** (355 mg, 1 mmol) and dimethyl maleate (**7**; 287 mg, 2 mmol), procedure *A*, reflux for 13 h. Yield: 217 mg (37%) of a yellowish solid. M.p. 185–188 °C. IR (KBr): 3393, 1750 (C=O), 1705

(C=O), 1668 (C=O), 1611. EIMS, *m/z*: 589 (MH^+). ^{1}H NMR (300 MHz, $CDCl_3$): 3.61, s, 3 H (OMe); 3.62, s, 3 H (OMe); 3.78, dd, 1 H, *J*(1,2) = 8.7, *J*(2,3) = 11.0 (H-2); 3.87, s, 3 H (OMe); 4.31, d, 1 H, *J*(5,6) = 12.1 (H-5); 4.50, d, 1 H, *J*(2,3) = 11.0 (H-3); 4.84, dd, 1 H, *J*(1,2) = 8.7, *J*(1,3) = 0.8 (H-1); 5.60, dd, 1 H, *J*(5,6) = 12.1, *J*(6,NH) = 8.7 (H-6); 6.51–6.56, m, 2 H (2 H of Ar); 6.61, d, 1 H, *J*(6,NH) = 8.7 (NH); 7.08–7.14, m, 2 H (2 H of Ar); 7.33–7.40, m, 4 H (4 H of Ar); 7.43–7.48, m, 1 H (1 H of Ar); 7.68–7.72, m, 2 H (2 H of Ar); 7.88–7.93, m, 2 H (2 H of Ar). ^{13}C NMR (75.5 MHz, DMSO-d_6): 53.2, 53.6, 55.8, 56.4, 57.1, 60.9, 70.0, 75.2, 114.1, 123.5, 127.7, 128.3, 129.1, 130.1, 130.8, 132.5, 134.5, 144.1, 147.8, 159.8, 162.9, 167.1, 168.6, 168.8. HRMS, *m/z*: calculated for $C_{30}H_{29}N_4O_9$ (MH^+) 589.1935, found 589.1941.

Dimethyl (1R,2S*,3R*,5R*,6R*)-6-benzamido-5-(4-methoxyphenyl)-7-oxo-3-(3,4,5-trimethoxyphenyl)hexahydropyrazolo[1,2-a]pyrazole-1,2-dicarboxylate* (**10c**). Prepared from dipole **6c** (490 mg, 1 mmol) and dimethyl maleate (**7**; 287 mg, 2 mmol), procedure *A*, reflux for 18 h. Yield: 134 mg (21%) of a white solid. M.p. 243–246 °C. IR (KBr): 3373, 1742 (C=O), 1707 (C=O), 1661 (C=O), 1595. ^{1}H NMR (300 MHz, $CDCl_3$): 3.63, s, 3 H (OMe); 3.64, s, 3 H (OMe); 3.68, s, 3 H (OMe); 3.70, s, 6 H (2 × OMe); 3.77, dd, 1 H, *J*(1,2) = 8.8, *J*(2,3) = 11.0 (H-2); 3.86, s, 3 H (OMe); 4.26, d, 1 H, *J*(5,6) = 12.2 (H-5); 4.30, d, 1 H, *J*(2,3) = 11.0 (H-3); 4.79, dd, 1 H, *J*(1,2) = 8.8, *J*(1,3) = 0.8 (H-1); 5.65, dd, 1 H, *J*(5,6) = 12.2, *J*(6,NH) = 8.4 (H-6); 6.35, s, 2 H (C_6H_2); 6.55–6.62, m, 2 H (2 H of Ar); 6.59, d, 1 H, *J*(6,NH) = 8.4 (NH); 7.13–7.17, m, 2 H (2 H of Ar); 7.35–7.42, m, 2 H (2 H of Ar); 7.44–7.50, m, 1 H (1 H of Ar); 7.69–7.74, m, 2 H (2 H of Ar). For $C_{33}H_{35}N_3O_{10}$ (633.65) calculated: C 62.55%, H 5.57%, N 6.63%; found: C 62.56%, H 5.70%, N 6.54%.

Dimethyl (1R,2S*,3R*,5R*,6R*)-6-benzamido-5-(1H-indol-3-yl)-7-oxo-3-phenylhexahydropyrazolo[1,2-a]pyrazole-1,2-dicarboxylate* (**10g**). Prepared from dipole **6a** (399 mg, 1 mmol) and dimethyl maleate (**7**; 287 mg, 2 mmol), procedure *B*, reflux for 14 h; CC: EtOAc. Yield: 376 mg (69%) of a white solid. M.p. 135–137 °C. IR (KBr): 3411, 1749 (C=O), 1696 (C=O), 1655 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$): 3.59, s, 3 H (OMe); 3.80, dd, 1 H, *J*(1,2) = 8.9, *J*(2,3) = 11.0 (H-2); 3.85, s, 3 H (OMe); 4.42, d, 1 H, *J*(2,3) = 11.0 (H-3); 4.72, d, 1 H, *J*(5,6) = 12.2 (H-5); 4.84, dd, 1 H, *J*(1,2) = 8.9, *J*(1,3) = 0.8 (H-1); 5.80, dd, 1 H, *J*(5,6) = 12.2, *J*(6,NH) = 8.3 (H-6); 6.70, d, 1 H, *J*(6,NH) = 8.3 (NH); 6.74–6.87, m, 3 H (3 H of Ar); 6.92, d, 1 H, *J*(1″,2″) = 2.6 (H-2″); 6.96–7.09, m, 4 H (4 H of Ar); 7.30–7.45, m, 4 H (4 H of Ar); 7.62–7.68, m, 2 H (2 H of Ar); 7.70–7.76, m, 1 H (1 H of Ar); 7.88, br d, 1 H, *J*(1″,2″) = 2.6 (H-1″). For $C_{31}H_{28}N_4O_6$ (552.58) calculated: C 67.38%, H 5.11%, N 10.14%; found: C 67.68%, H 5.33%, N 9.85%.

Dimethyl (1S,2R*,3S*,5R*,6R*)-6-benzamido-3-(2,6-dichlorophenyl)-5-(4-methoxyphenyl)-7-oxohexahydropyrazolo[1,2-a]pyrazole-1,2-dicarboxylate* (**11e**) *and its (1R*,2R*,3S*,5R*,6R*)-epimer* **12e**. Prepared from dipole **6e** (469 mg, 1 mmol) and dimethyl maleate (**7**; 287 mg, 2 mmol), procedure *B*, reflux for 17 h; CC: EtOAc–hexanes, 1:1.

Data for the major isomer **11e**. Yield: 115 mg (19%) of a white solid. M.p. 170–172 °C. IR (KBr): 3441, 1748 (C=O), 1707 (C=O), 1645 (C=O), 1614. ^{1}H NMR (300 MHz, $CDCl_3$): 3.66, s, 3 H (OMe); 3.75, s, 3 H (OMe); 3.85, s, 3 H (OMe); 4.25, d, 1 H, *J*(5,6) = 9.6 (H-5); 4.74, t, 1 H, *J*(1,2) ~ *J*(2,3) = 8.8 (H-2); 5.19, dd, 1 H, *J*(5,6) = 9.6, *J*(6,NH) = 8.0 (H-6); 5.25, d, 1 H, *J*(2,3) = 9.1 (H-3); 5.75, d, 1 H, *J*(1,2) = 8.5 (H-1); 6.50, d, 1 H, *J*(6,NH) = 8.0 (NH); 6.67–6.73, m, 2 H (2 H of Ar); 7.03–7.08, m, 2 H (2 H of Ar); 7.09–7.14, m, 2 H (2 H of Ar); 7.28–7.42, m, 3 H (3 H of Ar); 7.45–7.51, m, 1 H (1 H of Ar); 7.67–7.73, m, 2 H (2 H of Ar). For $C_{30}H_{27}Cl_2N_3O_7$ (612.46) calculated: C 58.83%, H 4.44%, N 6.86%; found: C 58.55%, H 4.56%, N 6.61%.

Data for the minor isomer **12e**. Yield: 61 mg (10%) of a white solid. M.p. 205–207 °C. IR (KBr): 3365, 1753 (C=O), 1722 (C=O), 1663 (C=O), 1611. ^{1}H NMR (300 MHz, $CDCl_3$): 3.65, s, 3 H (OMe); 3.66, s, 3 H (OMe); 3.85, s, 3 H (OMe); 4.18, dd, 1 H, *J*(1,2) = 4.9, *J*(2,3) = 9.1 (H-2); 4.65, d, 1 H, *J*(2,3) = 9.1 (H-3); 4.98, d, 1 H, *J*(5,6) = 11.7 (H-5); 5.29, d, 1 H, *J*(1,2) = 4.9 (H-1); 5.94, dd, 1 H, *J*(5,6) = 11.7, *J*(6,NH) = 9.0 (H-6); 6.48, d, 2 H, *J* = 8.8 (2 H of C_6H_4); 6.53, d, 1 H, *J*(6,NH) = 9.0 (NH); 6.85, dd, 1 H, *J* = 1.4, 8.1 (1 H of Ar); 6.92, t, 1 H, *J* = 7.9 (1 H of Ar); 7.14, dd, 1 H, *J* = 1.4, 7.9 (1 H of Ar); 7.31, br d, 2 H, *J* = 8.1 (2 H of Ar); 7.35–7.44, m, 3 H (3 H of Ar); 7.46–7.53, m, 1 H (1 H of Ar); 7.75–7.80, m, 1 H (1 H of Ar). For $C_{30}H_{27}Cl_2N_3O_7$ (612.46) calculated: C 58.83%, H 4.44%, N 6.86%; found: C 59.04%, H 4.62%, N 6.74%.

Dimethyl (1R,2R*,3S*,5R*,6R*)-6-benzamido-5-(4-methoxyphenyl)-7-oxo-3-(2,4,6-trimethylphenyl)hexahydropyrazolo[1,2-a]pyrazole-1,2-dicarboxylate* (**12d**).

Method A. Prepared in from dipole **6d** (442 mg, 1 mmol) and dimethyl maleate (**7**; 287 mg, 2 mmol), procedure *B*, reflux for 15 h; CC: EtOAc–hexanes, 2:1. Yield: 149 mg (25%) of a white solid. M.p. 197–200 °C. IR (KBr): 3411, 1747 (C=O), 1737 (C=O), 1668 (C=O), 1612. ^{1}H NMR (300 MHz, $CDCl_3$): 1.49, s, 3 H (Ar**Me**); 1.52, s, 3 H (Ar**Me**); 2.55, s, 3 H (Ar**Me**); 3.62, s, 3 H (OMe); 3.68, s, 3 H (OMe); 3.84, dd, 1 H, *J*(1,2) = 5.2, *J*(2,3) = 9.3 (H-2); 3.87, s, 3 H (OMe); 4.27, d, 1 H, *J*(2,3) = 9.3 (H-3); 4.79, d, 1 H, *J*(5,6) = 8.6 (H-5); 5.12, dd, 1 H, *J*(1,2) = 5.2 (H-1); 5.68, t, 1 H, *J*(5,6) = *J*(6,NH) = 8.6 (H-6); 6.40, br s, 1 H (1 H of C_6H_2); 6.55, d, 2 H, *J* = 8.7 (2 H of C_6H_4); 6.68, br s, 1 H (1 H of C_6H_2); 6.70, d, 1 H, *J*(6,NH) = 8.6 (NH); 7.13, d, 2 H, *J* = 8.7 (2 H of C_6H_4); 7.40–7.51, m, 3 H (3 H of Ar); 7.78–7.83, m, 2 H (2 H of Ar). For $C_{33}H_{35}N_3O_7$ (585.65) calculated: C 67.68%, H 6.02%, N 7.18%; found: C 67.78%, H 6.20%, N 7.15%.

Method B. Prepared in from dipole **6d** (442 mg, 1 mmol) and dimethyl fumarate (**8**; 287 mg, 2 mmol), procedure *B*, reflux for 7 h; CC: EtOAc–hexanes, 1:1. Yield: 199 mg (34%) of a white solid. Physical, analytical, and spectral data for compound **12d** are given above – see reaction of **6d** with dimethyl maleate (**7**).

Dimethyl (1R,2R*,3S*,5R*,6R*)-6-benzamido-3-(2,6-dichlorophenyl)-5-(4-methoxyphenyl)-7-oxohexahydropyrazolo[1,2-a]pyrazole-1,2-dicarboxylate* (**12e**). Prepared from dipole **6e** (469 mg, 1 mmol) and dimethyl fumarate (**8**; 287 mg, 2 mmol), procedure *A*, reflux for 5h. Yield: 329 mg (54%) of a white solid. Physical and spectral data for compound **12e** are given above – see reaction of **6e** with dimethyl maleate (**7**).

Dimethyl (1R,2R*,3S*,5R*,6R*)-6-benzamido-3-(2,6-dichlorophenyl)-5-(1H-indol-3-yl)-7-oxohexahydropyrazolo[1,2-a]pyrazole-1,2-dicarboxylate* (**12j**) *and its (1S*,2S*,3R*,5R*,6R*)-epimer* **13j**. Prepared from dipole **6j** (477 mg, 1 mmol) and dimethyl fumarate (**8**; 287 mg, 2 mmol), procedure *B*, reflux for 11 h; CC: EtOAc–hexanes, 1:1.

Data for the minor isomer **12j**. Yield: 87 mg (14%) of a white solid. M.p. 188–190 °C. IR (KBr): 3227, 1739 (C=O), 1660 (C=O), 1638 (C=O). EIMS, *m/z*: 620 (M^+). ^{1}H NMR (300 MHz, $CDCl_3$): 3.66, s, 3 H (OMe); 3.88, s, 3 H (OMe); 4.24, dd, 1 H, *J*(1,2) = 4.5, *J*(2,3) = 9.2 (H-2); 4.75, d, 1 H, *J*(5,6) = 9.2 (H-3); 5.21, d, 1 H, *J*(2,3) = 11.7 (5-H); 5.37, d, 1 H, *J*(1,2) = 4.5 (H-1); 6.01, dd, 1 H, *J*(5,6) = 9.2, *J*(6,NH) = 8.0 (H-6); 6.43, d, 1 H, *J*(6,NH) = 8.0 (NH); 6.55–6.63, m, 2 H (2 H of Ar); 6.83–6.90, m, 1 H (1 H of Ar); 6.90–6.98, m, 2 H (2 H of Ar); 7.32–7.55, m, 5 H (5 H of Ar); 7.67–7.75, m, 3 H (3 H of Ar); 8.01, s, 1 H (H-1″). ^{13}C NMR (75.5 MHz, DMSO-d_6): 50.3, 53.5, 53.7, 54.3, 59.6, 64.3, 79.3, 79.8, 80.2, 107.3, 119.1, 119.2, 122.0, 125.1, 127.5, 128.1, 129.0, 129.2, 130.6, 134.0, 134.2, 134.9, 137.1, 167.2, 170.2, 171.8, 177.4. HRMS, *m/z*: calculated for $C_{31}H_{26}Cl_2N_4O_6$ (M^+) 620.1229, found 620.1234.

Data for the major isomer **13j**. Yield: 112 mg (18%) of yellow oil. IR (NaCl): 3285, 1742 (C=O), 1656 (C=O). EIMS, *m/z*: 620 (M^+). ^{1}H NMR (300 MHz, $CDCl_3$): 3.77, s, 3 H (OMe); 3.82, s, 3 H (OMe); 4.45, dd, 1 H, *J*(1,2) = 4.5, *J*(2,3) = 9.0 (H-2); 4.85, d, 1 H, *J*(5,6) = 8.7 (H-5); 5.12, d, 1 H, *J*(2,3) = 9.0 (3-H); 5.42, d, 1 H, *J*(1,2) = 4.5 (H-1); 5.92, t, 1 H, *J*(5,6) = *J*(6,NH) = 8.7 (H-6); 6.15, d, 1 H, *J*(6,NH) = 8.7 (NH); 6.90, ddd, 1 H, *J* = 1.1, 7.2, 9.0 (1 H of Ar); 7.03–7.10, m, 2 H (2 H of Ar); 7.13–7.20, m, 3 H (3 H of Ar); 7.30–7.35, m, 4 H (4 H of Ar); 7.43–7.50, m, 3 H (3 H of Ar); 8.20, s, 1 H (H-1″). ^{13}C NMR (75.5 MHz, DMSO-d_6): 52.6, 52.9, 53.3, 56.3, 57.4, 66.6, 78.2, 78.6, 79.0, 109.6, 110.9, 118.2, 120.4, 124.1, 127.4, 127.8, 128.0, 129.4, 130.5, 134.0, 134.7, 135.7, 136.7, 167.3, 169.1, 170.3, 172.0. HRMS, *m/z*: calculated for $C_{31}H_{26}Cl_2N_4O_6$ (M^+) 620.1229, found 620.1245.

Methyl (1R,3R*,5R*,6R*)-6-benzamido-5-(4-methoxyphenyl)-7-oxo-3-phenylhexahydropyrazolo-[1,2-a]pyrazole-1,2-dicarboxylate* (**14a**) *and its (1S*,3S*,5R*,6R*)-isomer* **15a**. Prepared from dipole **6a** (399 mg, 1 mmol) and methyl acrylate (**9**; 172 mg, 2 mmol), procedure *B*, reflux for 10 h; CC: EtOAc–hexanes, 2:1.

Data for the major isomer **14a**. Yield: 161 mg (37%) of a white solid. M.p. 203–204 °C. IR (KBr): 3335, 1742 (C=O), 1708 (C=O), 1644 (C=O), 1611. ^{1}H NMR (300 MHz, $CDCl_3$): 2.58, ddd, 1 H, *J*(1,2a) = 1.1, *J*(2a,3) = 5.5, *J*(2a,2b) = 13.2 (Ha-2); 2.78, ddd, 1 H, *J*(1,2b) = 9.4, *J*(2b,3) = 11.5, *J*(2a,2b) = 13.2 (Hb-2); 3.64, s, 3 H (OMe); 3.90, s, 3 H (OMe); 4.05, d, 1 H, *J*(2a,3) = 5.5, *J*(2b,3) = 11.5 (H-3); 4.20, d, 1 H, *J*(5,6) = 12.1 (H-5); 4.57, br d, 1 H, *J*(1,2b) = 9.4 (H-1); 5.54, dd, 1 H, *J*(5,6) = 12.1, *J*(6,NH) = 8.7 (H-6); 6.50–6.56, m, 2 H (2 H of Ar); 6.64, d, 1 H, *J*(6,NH) = 8.7 (NH); 7.00–7.05, m, 1 H (1 H of Ar); 7.01–7.06, m, 2 H (2 H of Ar); 7.07–7.14, m, 4 H (4 H of Ar); 7.32–7.40, m, 2 H (2 H of Ar); 7.42–7.49, m, 1 H (1 H of Ar); 7.70–7.75, m, 2 H (2 H of Ar). For $C_{28}H_{27}N_3O_5$ (485.53) calculated: C 69.26%, H 5.61%, N 8.65%; found: C 69.38%, H 5.72%, N 8.62%.

Data for the minor isomer **15a**. Yield: 29 mg (7%) of a white solid. M.p. 109–114 °C. IR (KBr): 3447, 1717 (C=O), 1648 (C=O), 1615. EIMS, *m/z*: 485 (M^+). ^{1}H NMR (300 MHz, $CDCl_3$): 2.40, ddd, 1 H, *J*(1,2a) = 6.6, *J*(2a,3) = 9.1, *J*(2a,2b) = 13.2 (Ha-2); 2.95, ddd, 1 H, *J*(1,2b) = 9.8, *J*(2b,3) = 7.4, *J*(2a,2b) = 13.2 (Hb-2); 3.50, s, 3 H (OMe); 3.68, dd, 1 H, *J*(2a,3) = 9.1, *J*(2b,3) = 7.4 (H-3); 3.84, s, 3 H (OMe); 4.70, dd, 1 H, *J*(1,2a) = 6.6, *J*(1,2b) = 9.8 (H-1); 4.80, d, 1 H, *J*(5,6) = 8.5 (H-5); 5.60, t, 1 H, *J*(5,6) = *J*(6,NH) = 8.5 (H-6); 6.60, d, 2 H, *J* = 8.8 (2 H of Ar); 6.88, d, 1 H, *J*(6,NH) = 8.5 (NH); 6.93–6.99, m, 2 H (2 H of Ar); 7.01–7.07, m, 2 H (2 H of Ar); 7.08–7.14, m, 2 H (2 H of Ar); 7.30–7.45, m, 3 H (3 H of Ar); 7.46–7.52, m, 1 H (1 H of Ar); 7.78–7.83, m, 2 H (2 H of Ar). ^{13}C NMR (75.5 MHz, DMSO-d_6): 42.7, 53.4, 54.7, 55.4, 55.6, 63.2, 65.2, 114.0, 124.6, 127.7, 127.8, 128.0, 128.4, 128.8, 130.6, 132.2, 133.8, 138.5, 160.0, 167.8, 171.0, 171.7. HRMS, *m/z*: calculated for $C_{28}H_{27}N_3O_5$ (M^+) 485.1951, found 485.1961.

Methyl (1R,3R*,5R*,6R*)-6-benzamido-5-(4-methoxyphenyl)-3-(4-nitrophenyl)-7-oxohexahydro-pyrazolo[1,2-a]pyrazole-1,2-dicarboxylate* (**14b**). Prepared from dipole **6a** (399 mg, 1 mmol) and methyl acrylate (**9**; 172 mg, 2 mmol), procedure *A*, reflux for 11 h. Yield: 343 mg (65%) of a white solid. M.p. 221–224 °C. IR (KBr): 3459, 1750 (C=O), 1705 (C=O), 1645 (C=O), 1611. ^{1}H NMR (300 MHz, $CDCl_3$): 2.64, ddd, 1 H, *J*(1,2a) = 1.0, *J*(2a,3) = 5.7, *J*(2a,2b) = 13.2 (Ha-2); 2.72, ddd, 1 H, *J*(1,2b) = 8.7, *J*(2b,3) = 11.2, *J*(2a,2b) = 13.2 (Hb-2); 3.62, s, 3 H (OMe); 3.91, s, 3 H (OMe); 4.20, d, 1 H, *J*(2a,3) = 5.7, *J*(2b,3) = 11.2 (H-3); 4.22, d, 1 H, *J*(5,6) = 12.0 (H-5); 4.59, dd, 1 H, *J*(1,2a) = 1.0, *J*(1,2b) = 8.7 (H-1); 5.57, dd, 1 H, *J*(5,6) = 12.0, *J*(6,NH) = 8.1 (H-6); 6.52–6.58, m, 2 H (2 H of Ar); 6.65, d, 1 H, *J*(6,NH) = 8.1 (NH); 7.11–7.17, m, 2 H (2 H of Ar); 7.27–7.41, m, 4 H (4 H of Ar); 7.45–7.49, m, 1 H (1 H of Ar);

7.70–7.75, m, 2 H (2 H of Ar); 7.88–7.94, m, 2 H (2 H of Ar). For $C_{28}H_{26}N_4O_7$ (530.53) calculated: C 63.39%, H 4.94%, N 10.56%; found: C 63.24%, H 5.02%, N 10.38%.

Methyl (1R,3R*,5R*,6R*)-6-benzamido-5-(4-methoxyphenyl)-7-oxo-3-(3,4,5-trimethoxyphenyl)-hexahydropyrazolo[1,2-a]pyrazole-1,2-dicarboxylate* (**14c**). Prepared from dipole **6c** (490 mg, 1 mmol) and methyl acrylate (**9**; 172 mg, 2 mmol), procedure *A*, reflux for 11 h. Yield: 346 mg (65%) of a white solid. M.p. 124–125 °C. IR (KBr): 3324, 1744 (C=O), 1704 (C=O), 1665 (C=O), 1595. EIMS, *m/z*: 575 (M^+). ^{1}H NMR (300 MHz, $CDCl_3$): 2.57, ddd, 1 H, *J*(1,2a) = 0.7, *J*(2a,3) = 5.4, *J*(2a,2b) = 13.2 (Ha-2); 2.72, ddd, 1 H, *J*(1,2b) = 9.0, *J*(2b,3) = 11.3, *J*(2a,2b) = 13.2 (Hb-2); 3.65, s, 3 H (OMe); 3.69, s, 3 H (OMe); 3.70, s, 6 H (2 × OMe); 3.90, s, 3 H (OMe); 4.01, d, 1 H, *J*(2a,3) = 5.4, *J*(2b,3) = 11.3 (H-3); 4.18, d, 1 H, *J*(5,6) = 12.0 (H-5); 4.54, br d, 1 H, *J*(1,2b) = 9.0 (H-1); 5.58, dd, 1 H, *J*(5,6) = 12.0, *J*(6,NH) = 8.3 (H-6); 6.33, s, 2 H (C_6H_2); 6.58, d, 2 H, *J* = 8.7 (2 H of Ar); 6.72, d, 1 H, *J*(6,NH) = 8.3 (NH); 7.10–7.18, m, 3 H (3 H of Ar); 7.32–7.40, m, 2 H (2 H of Ar); 7.72–7.76, m, 2 H (2 H of Ar). ^{13}C NMR (75.5 MHz, DMSO-d_6): 42.6, 53.0, 53.6, 54.9, 55.9, 60.5, 60.8, 68.7, 104.4, 113.2, 127.1, 127.2, 128.1, 128.2, 129.3, 131.5, 131.6, 133.2, 137.4, 152.7, 159.3, 163.1, 167.0, 170.2. HRMS, *m/z*: calculated for $C_{31}H_{33}N_3O_8$ (M^+) 575.2268, found 575.2278.

Methyl (1R,3R*,5R*,6R*)-6-benzamido-5-(1H-indol-3-yl)-7-oxo-3-phenylhexahydropyrazolo-[1,2-a]pyrazole-1,2-dicarboxylate* (**14g**). Prepared from dipole **6g** (408 mg, 1 mmol) and methyl acrylate (**9**; 172 mg, 2 mmol), procedure *B*, reflux for 8 h; CC: EtOAc–hexanes, 2:1. Yield: 314 mg (64%) of a white solid. M.p. 138–140 °C. IR (KBr): 3304, 1744 (C=O), 1691 (C=O), 1655 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$): 2.60, ddd, 1 H, *J*(1,2a) = 1.1, *J*(2a,3) = 5.7, *J*(2a,2b) = 13.2 (Ha-2); 2.76, ddd, 1 H, *J*(1,2b) = 9.1, *J*(2b,3) = 11.3, *J*(2a,2b) = 13.2 (Hb-2); 3.91, s, 3 H (OMe); 4.13, dd, 1 H, *J*(2a,3) = 5.7, *J*(2b,3) = 11.3 (H-3); 4.59, br d, 1 H, *J*(1,2b) = 9.1 (H-1); 4.63, d, 1 H, *J*(5,6) = 12.1 (H-5); 5.75, dd, 1 H, *J*(5,6) = 12.1, *J*(6,NH) = 8.2 (H-6); 6.68, d, 1 H, *J*(6,NH) = 8.2 (NH); 6.80–6.90, m, 3 H (3 H of Ar); 6.93–7.10, m, 5 H (5 H of Ar); 7.30–7.42, m, 3 H (3 H of Ar); 7.67–7.74, m, 4 H (4 H of Ar); 7.82, s, 1 H (H-1′′). For $C_{29}H_{26}N_4O_4$ (494.54) calculated: C 70.43%, H 5.30%, N 11.33%; found: C 70.57%, H 5.48%, N 11.13%.

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