Combinatorial Solution-Phase Synthesis of Alkyl (1*S**,2*S**,3*R**,5*R**,6*R**)-1-Alkyl-3-aryl-6-benzoylamino-1-hydroxy-7-oxo-5-phenylhexahydropyrazolo[1,2-*a*]pyrazole-2-carboxylates

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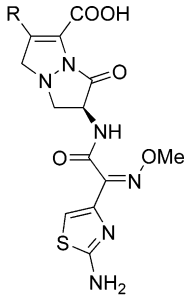
Combinatorial solution-phase cycloadditions of (1*Z*,4*R**,5*R**)-4-benzoylamino-5-phenylpyrazolidin-3-on-1-azomethine imines **3** to β-keto esters **4** afforded a library of 26 bicyclic pyrazolidinones **5** in 6−89% yields and in 14−100% de. All products were isolated in >90% purity according to ^{1}H NMR, and 25 of them were analytically pure. The structures of cycloadducts were confirmed by NMR and X-ray diffraction. Most of the products were isolated as mixtures of the major (1*S**,2*S**,3*R**,5*R**,6*R**)-epimers **5** and the minor (1*R**,2*S**,3*R**,5*R**,6*R**)-epimers **6**. Epimerization of cycloadducts **5/6** at the anomeric position 1 in solution was confirmed by ^{1}H NMR.

Introduction

Various functionalized monocyclic, fused, and spiro heterocycles represent important scaffolds for the preparation of compound libraries for medicinal and pharmaceutical applications because of their ability to mimic structures of peptides and reversibly bind proteins.[1−8] 1,3-Dipolar cycloadditions are useful reactions for the preparation of five-membered heterocycles because they enable access to polyfunctional compounds with multiple asymmetric centers, usually with excellent stereocontrol.[9] In combinatorial synthesis, [3+2] cycloadditions are also the most-studied cycloadditions, which have been shown to comprise a wide range of dipolarophiles and dipoles, such as azides, nitrones, nitrile oxides, and azomethine ylides.[10] However, many fewer examples of combinatorial cycloadditions have been reported in the azomethine imine series.[11−17]

Pyrazolidin-3-ones and pyrazolo[1,2-*a*]pyrazolones are interesting compounds because several of their derivatives exhibit biological activities and have applicability in industrial processes.[18,19] Examples of pyrazolo[1,2-*a*]pyrazolone based peptidomimetics[8] are Eli-Lilly's γ-lactam antibiotics LY 186826, LY 193239, and LY 255262 (Figure 1).[20−26] Since the first reports of Dorn[27−29] and Oppolzer,[30,31] 1,3-dipolar cycloaddition of pyrazolidin-3-one derived azomethine imines to acetylenic and olefinic dipolarophiles represents a common method for the preparation of pyrazolo[1,2-*a*]pyrazolones. Most of the early studies were performed on achiral and monosubstituted chiral dipoles,[18−32] while recent studies established the applicability of chiral polysubstituted 3-pyrazolidinone-1-azomethine imines in the stereoselective synthesis of highly functionalized pyrazolo[1,2-*a*]pyrazolones.[15,17,33−41]



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

Figure 1.

Our studies on the synthesis of functionalized heterocycles[40−50] were recently extended to the combinatorial synthesis of heterocyclic α-amino acid[51−53] and dipeptide analogs.[17,54] In connection with our work on chiral azomethine imines,[15,17,33,38,40−45] we have recently reported stereocontrol in 1,3-dipolar cycloadditions of (1Z,4*R**,5*R**)-1-arylmethylidene-4-benzoylamino-5-phenylpyrazolidin-3-on-1-azomethine imines **3** to acyclic olefinic dipolarophiles, where the regiochemistry and stereochemistry were controlled by the stereodirecting phenyl group at position 5, by the structure of the dipolarophile, and by the *ortho* substituents at the aromatic ring.[38] These results indicated that dipoles **3** could be useful substrates for combinatorial synthesis of 2-amino-1-oxopyrazolo[1,2-*a*]pyrazole-7-carboxylates with variable substitution pattern and variable, yet predictable, configuration. Recently, we reported a stereoselective solution-phase combinatorial synthesis of 1,6,7,9-tetrasubstituted 6,7,9,9a-tetrahydro-5*H*-pyrazolo[1,2-*a*]pyrrolo[3,4-*c*]pyrazole-1,3,5(2*H*,3a*H*)-triones based on 1,3-dipolar cycloadditions of azomethine imines **3** to N-substituted

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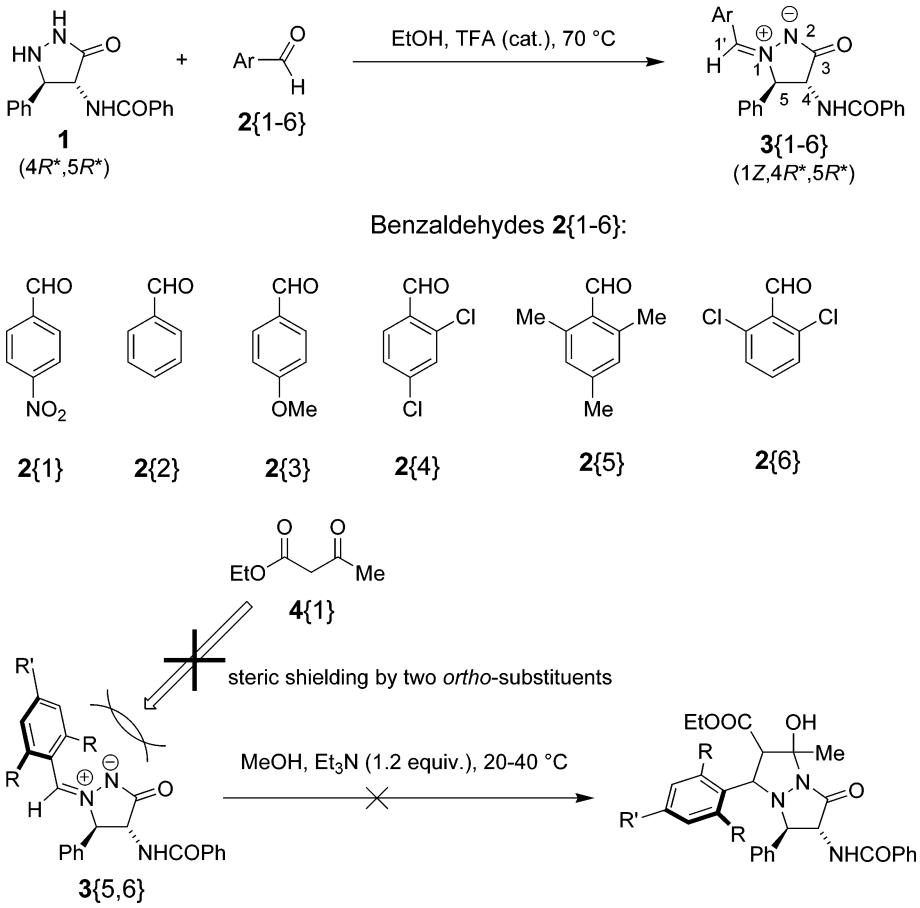
Scheme 1



maleimides.[17] In continuation, we focused our attention on base-catalyzed cycloadditions of dipoles **3** to β-keto esters **4**, which were quite unexplored, since only two examples were reported previously in the literature.[33] Herein, we report a combinatorial stereoselective solution-phase synthesis of 1-substituted alkyl (1*S**,2*S**,3*R**,5*R**,6*R**)-3-aryl-6-benzoylamino-1-hydroxy-7-oxo-5-phenylhexahydropyrazolo[1,2-*a*]-pyrazole-2-carboxylates **5** by cycloadditions of azomethine imines **3**{*1*−*4*} to β-keto esters **4**{*1*−*9*}.

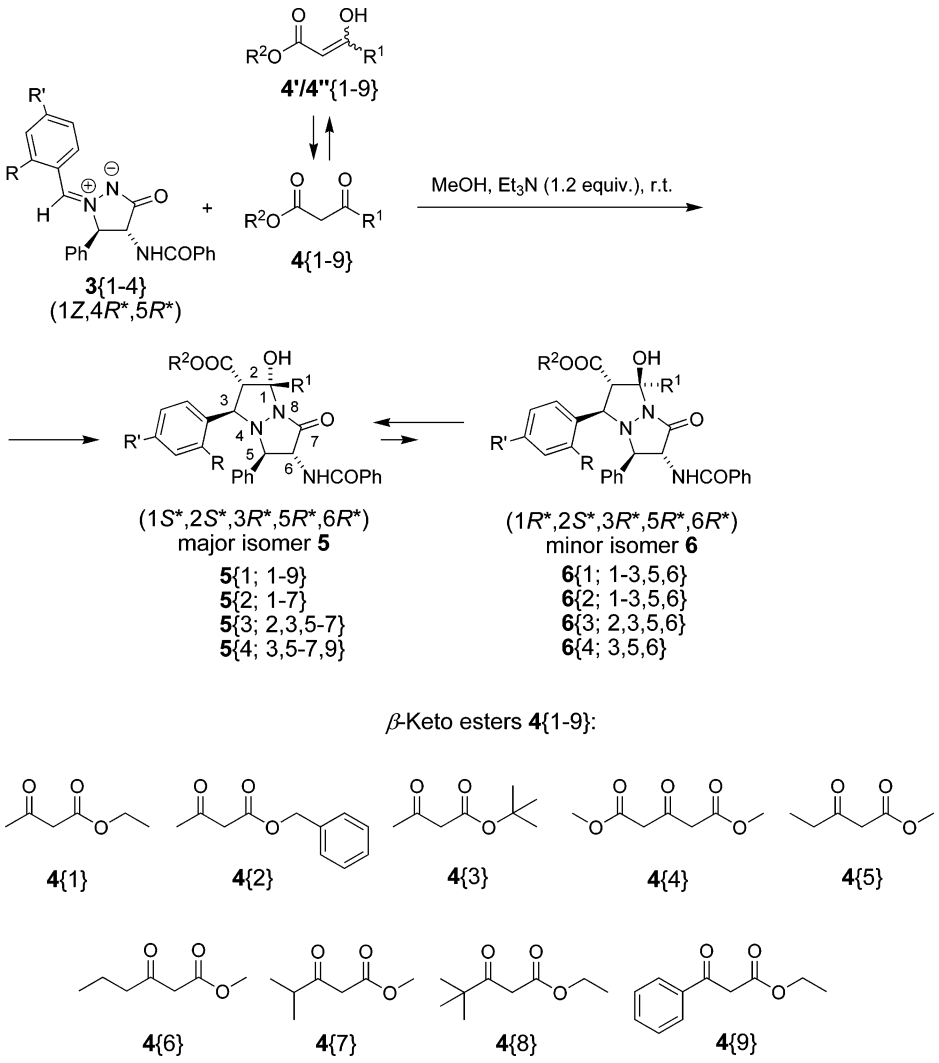
Results and Discussion

First, stable azomethine imines **3**{*1*−*6*} were synthesized in a parallel manner from (4*R**,5*R**)-4-benzoylamino-5-phenyl-3-pyrazolidinone (**1**) and substituted benzaldehydes **2**{1−6} according to the previously published general methodology.[17,38] All dipoles **3**{*1*−*6*} were formed as precipitates and were isolated in good yields by filtration, washing with ether, and drying. The purity of all dipoles was >90% according to ^{1}H NMR (Scheme 1).

Since both previously reported 1,3-dipolar cycloadditions to methyl and ethyl acetoacetate were carried out with the *ortho*-unsubstituted azomethine imine **3**{*1*},[33] we tested the *ortho*-disubstituted dipoles **3**{*5,6*} for their reactivity toward β-keto esters prior to combinatorial study. Much to our disappointment, the dipoles **3**{*5,6*} did not react with ethyl acetoacetate **4**{*1*} in methanol in the presence of triethylamine at room temperature (RT). At slightly elevated temperature (40 °C), partial decomposition of azomethine imines **3**{*5,6*} was observed. This can be rationalized by the steric hindrance of the reactive site (1,3-dipole) by two *ortho*-substituents at the aryl residue, which prevent the approach of the dipolarophile **4** (Scheme 1).

The *ortho*-unsubstituted dipoles **3**{*1*−*3*} and the *ortho*-monosubstituted dipole **3**{*4*} were then chosen as the model dipoles for the combinatorial study. Azomethine imines **3**{*1*−*4*} were treated with commercially available β-keto esters **4**{*1*−*9*} in methanol in the presence of triethylamine at RT in a parallel synthesizer. Within the set of 36 reactions, 26 of them gave the corresponding cycloadducts, 1-substituted alkyl (1*S**,2*S**,3*R**,5*R**,6*R**)-3-aryl-6-benzoylamino-1-hydroxy-7-oxo-5-phenyl-hexahydropyrazolo[1,2-*a*]pyrazole-2-carboxylates **5** in 6−89% yields and in 14−100% de. No conversion was detected by TLC for 10 reactions. All 26 products **5/6** precipitated from the reaction mixtures and were isolated by filtration, washing with ether, and drying in vacuo. Upon this simple workup protocol, 20 compounds, **5/6**{*1*; *1*−*3,5,6*}, **5**{*1*; *4,7*−*9*}, **5/6**{*2*; *1*−*3,5*}, **5**{*2*; *4,7*}, **5/6**{*3*; *2,3*}, **5**{*3*; *7*}, **5/6**{*4*; *3*}, and **5**{*4*; *7*}, were >90% pure, while six compounds, **5**{*1*; *8*}, **5/6**{*2*; *6*}, **5/6**{*3*; *5,6*}, and **5**{*4*; *6,9*}, were contaminated with the unreacted azomethine imine **3** and were further purified by flash chromatography. Finally, 25 products were obtained as white solids in analytical purity, while compound **5**{*1*; *9*} was obtained as a yellow oil in >90% purity according to ^{1}H NMR. In terms of isomeric purity, 17 compounds, **5/6**{*1*; *1*−*3,5,6*}, **5/6**{*2*; *1*−*3,5,6*}, **5/6**{*3*; *2,3,5,6*}, and **5/6**{*4*; *3*}, were obtained as mixtures of the major (1*S**,2*S**,3*R**,5*R**,

Scheme 2



6*R**)-epimers **5** and the minor (1*R**,2*S**,3*R**,5*R**,6*R**)-epimers **6**, while 9 compounds, **5**{*1*,*2*; *4*}, **5**{*1*−*4*; *7*}, **5**{*1*, *8*}, and **5**{*1*,*4*; *9*}, were obtained as pure (1*S**,2*S**,3*R**, 5*R**,6*R**)-isomers **5** (Scheme 2, Table 1).

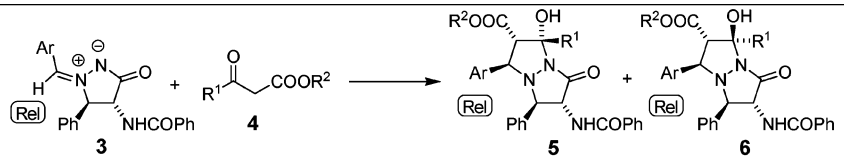
Stereochemistry and the mechanism of cycloadditions could be explained according to the previously proposed stereocontrol in cycloadditions of *ortho*-unsubstituted dipoles **3** to acyclic olefinic dipolarophiles.[38] Dipoles **3**{*1*−*4*} with at least one free *ortho*-position in the aromatic ring can adopt the planar conformation **3′**{*1*−*4*} allowing the transition state for the concerted 1,3-dipolar cycloaddition. The *endo* approach of the isomeric dipolarophiles **4′** and **4″** from the less-hindered face of the (1*Z*,4*R**,5*R**)-dipole **3′** then leads to a mixture of epimeric cycloadducts **5** and **6**, respectively (Scheme 3). At the first glance, stereoselectivity of most cycloadditions was only moderate with a typical isomer ratio of ∼85:15. However, isomeric cycloadducts **5** and **6** differed only by the configuration at C(1), while the configurations at the other newly formed chiral centers at C(2) and C(3) in all compounds **5** and **6** were the same. Position 1 is analogous to the anomeric position in carbohydrates, which readily epimerize in solution. Thus, formation of two epimers **5** and **6** could be rationalized, either by *Z*/*E*-isomerization of the dipolarophile **4′**/**4″** via the β-keto ester tautomeric form **4** or by equilibration between epimeric hemiaminals **5** and **6** in solution via the ring-opened intermediate **7**. In both cases, stabilization by the intramolecular C═O···H−O bond should favor the formation of the major (1*S**,2*S**,3*R**,5*R**, 6*R**)-isomers **5**. Isomerization of compounds **5**/**6**{*4*; *3*} and **5**{*2*; *7*} at the anomeric center C(1) in DMSO-d_6 solution was confirmed by ^{1}H NMR (Scheme 3, for the epimerization data see Supporting Information).

The structures of all novel compounds **5**/**6** were determined by spectroscopic methods (IR, ^{1}H and ^{13}C NMR, NOESY spectroscopy, MS, HRMS) and by elemental analyses for C, H, and N. The relative configurations of cycloadducts **5** and **6** were determined by NOESY spectroscopy, by correlation of chemical shifts for *H*−C(2), *H*−C(3), *H*−C(5), *H*−C(6), and H−N, and by correlation of vicinal coupling constants,$^3J_{H2-H3}$ and$^3J_{H5-H6}$. The structure of compound **5**{*2*; *4*} was determined by X-ray diffraction. A detailed description of structure determination is given in the Supporting Information.

Conclusion

Combinatorial solution-phase cycloadditions of (1*Z*,4*R**, 5*R**)-4-benzoylamino-5-phenylpyrazolidin-3-on-1-azomethine imines **3**{*1*−*4*} to β-keto esters **4**{*1*−*9*} afforded a library of 26 cycloadducts upon simple workup. All products were isolated in >90% purity according to ^{1}H NMR, 25 of

Table 1. Experimental Data for Cycloadducts **5** and **6** Obtained in Reactions of Azomethine Imines **3**{*1*−*4*} with *β*-Keto Esters **4**{*1*−*9*}[a]



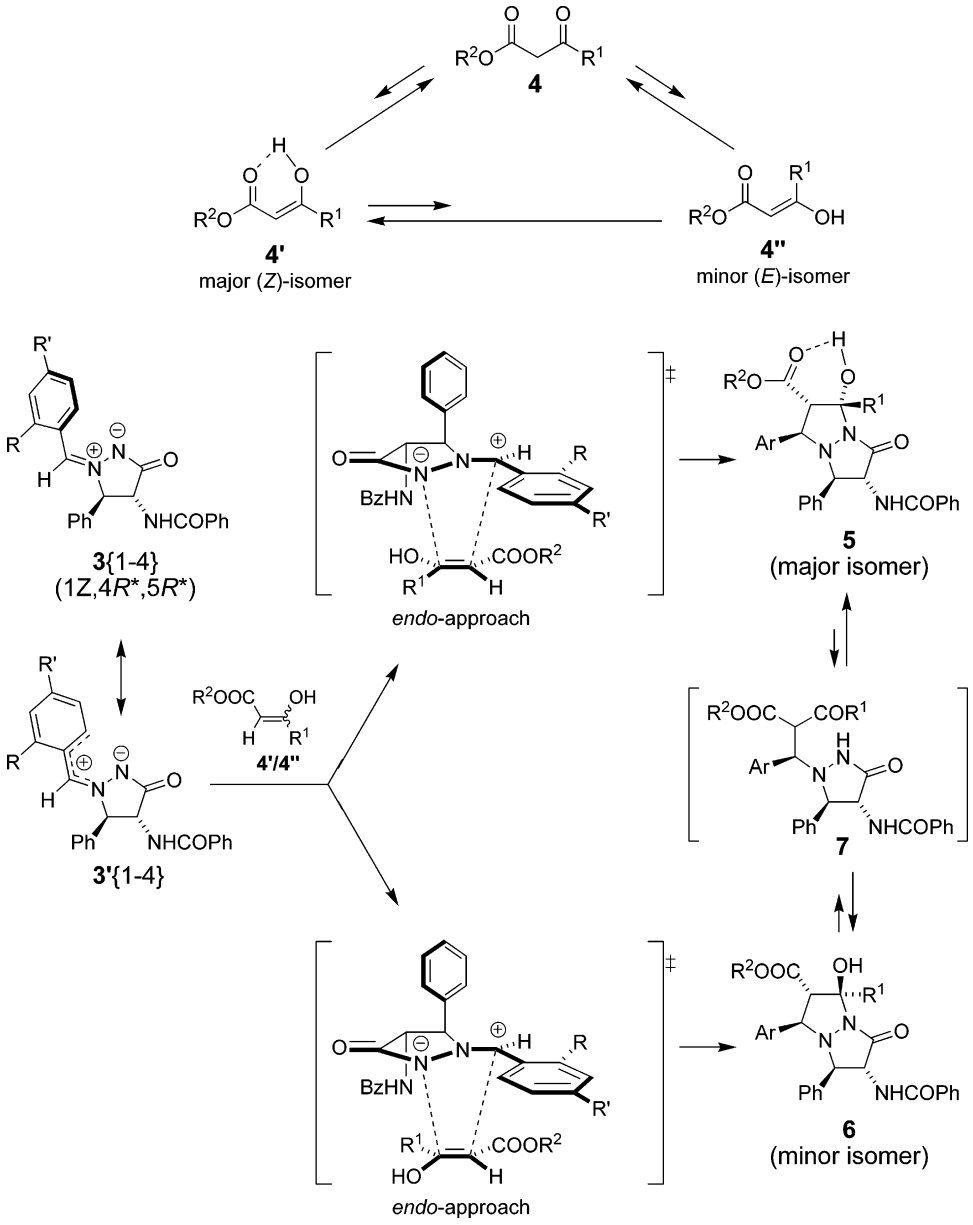
Products **5/6**

Yield (%) (Ratio of Isomers)

↓*β*-Keto Ester **4** (R^1, R^2)↓	← Azomethine Imine **3** (Ar) →			
	3{1}	**3**{2}	**3**{3}	**3**{4}
4{1}	**5/6**{1; 1} 75 (**5**:**6** = 81:19)	**5/6**{2; 1} 76 (**5**:**6** = 74:26)	0[b]	0[b]
4{2}	**5/6**{1; 2}[c] 89 (**5**:**6** = 80:20)	**5/6**{2; 2} 60 (**5**:**6** = 57:43)	**5/6**{3; 2} 34 (**5**:**6** = 58:42)	0[b]
4{3}	**5/6**{1; 3} 86 (**5**:**6** = 93:7)	**5/6**{2; 3} 78 (**5**:**6** = 73:27)	**5/6**{3; 3} 80 (**5**:**6** = 84:16)	**5/6**{4; 3} 66 (**5**:**6** = 88:12)
4{4}	**5**{1; 4} 86 (**5**:**6** = 100:0)	**5**{2; 4} 76 (**5**:**6** = 100:0)	0[b]	0[b]
4{5}	**5/6**{1; 5} 85 (**5**:**6** = 93:7)	**5/6**{2; 5} 60 (**5**:**6** = 86:14)	**5/6**{3; 5} 29 (**5**:**6** = 86:14)[d]	**5/6**{4; 5} 44 (**5**:**6** = 88:12)
4{6}	**5/6**{1; 6} 85 (**5**:**6** = 90:10)	**5/6**{2; 6} 19 (**5**:**6** = 91:9)[d]	**5/6**{3; 6} 22 (**5**:**6** = 87:13)[d]	**5/6**{4; 6} 54 (**5**:**6** = 84:16)[d]
4{7}	**5**{1; 7} 49 (**5**:**6** = 100:0)	**5**{2; 7} 32 (**5**:**6** = 100:0)	**5**{3; 7} 43 (**5**:**6** = 100:0)	**5**{4; 7} 23 (**5**:**6** = 100:0)
4{8}	**5**{1; 8} 41 (**5**:**6** = 100:0)[d]	0[b]	0[b]	0[b]
4{9}	**5**{1; 9}[e] 14 (**5**:**6** = 100:0)	0[b]	0[b]	**5**{4; 9} 6 (**5**:**6** = 100:0)[d]

[a] All products were obtained in >90% purity according to ^{1}H NMR and elemental analyses. Unless otherwise stated, the values found for C, H, and N were within ±0.4% with respect to the theoretical values. [b] No conversion was detected by TLC. [c] The value for C was within ±0.5% range with respect to the theoretical values. [d] Upon chromatographic purification (FC). [e] Identity was confirmed by MS and ^{13}C NMR.

Scheme 3



them were analytically pure. Stereocontrol of cycloadditions was the same as that established previously in cycloadditions of *ortho*-unsubstituted dipoles **3**{*1*−*3*} to acyclic olefinic dipolarophiles.[38] The anomeric center at C(1) allows epimerization of **5**/**6** in solution, and consequently, most of the products were obtained as mixtures of the major (1*S**)-epimers **5** and the minor (1*R**)-epimers **6**. In conclusion, this synthetic methodology might offer an easy access to diversity-oriented libraries of polysubstituted 1-hydroxyhexahydropyrazolo[1,2-*a*]pyrazolones in search for novel bioacative compounds.

Experimental Section

Melting points were determined on a Kofler micro hot stage. The NMR spectra were obtained on a Bruker Avance DPX 300 at 300 MHz for ^{1}H and 75.5 MHz for ^{13}C nucleus, using DMSO-d_6 and $CDCl_3$ with TMS as the internal standard, as solvents. Mass spectra were recorded on an AutoSpecQ spectrometer, and the IR spectra were recorded on a Perkin-Elmer Spectrum BX FT-IR spectrophotometer. Microanalyses were performed on a Perkin-Elmer CHN Analyzer 2400. Column chromatography 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 **2**{*1*−*6*} and β-keto esters **4**{*1*−*9*} are commercially available (Sigma-Aldrich). (4*R**,5*R**)-4-Benzoylamino-5-phenylpyrazolidin-3-one (**1**) and azomethine imines **3**{*1*−*6*} were prepared according to the literature procedures.[17,33,38]

Parallel synthesis of azomethine imines **3**{*1*−*6*} and combinatorial cycloadditions of dipoles **3**{*1*−*6*} to β-keto esters **4**{*1*−*9*} were carried out on a Mettler-Toledo Bohdan MiniBlock Compact Shaking and Washing Station and Vacuum Collection Base (12 positions, Vortex stirring, 400 rpm in all cases).

General Procedure for the Preparation of Azomethine Imines 3{1−6}. Compounds **3**{*1*−*6*} were prepared from **1** and aldehydes **2**{*1*−*6*} according to a slightly modified

literature procedure.[17] MiniBlock was equipped with 6 fritted vessels and charged with pyrazolidinone **1** (6 × 0.843 g, 6 × 3 mmol), anhydrous ethanol (6 × 12 mL), and benzaldehydes **2**{*1*−*6*} (3.6 mmol of each). The reaction mixtures were vortexed at RT for 5 min; trifluoroacetic acid was added (6 × 6 drops), and vortexing was continued at 75 °C for 1.5 h. Then the reaction mixtures were cooled to 0 °C. The precipitates were collected by filtration, washed with Et_2O (6 × 10 mL), and dried in vacuo to give the azomethine imines **3**{*1*−*6*}. The yields and physical and spectral data for known compounds **3**{*1*−*3*,*5*,*6*} were identical to those reported in the literature for the conventional single-vessel synthesis of **3**{*1*−*3*,*6*}[33] and **3**{*5*}.[38] The following compounds were prepared in this manner.

(1*Z*,4*R,5*R**)-4-Benzoylamino-1-(4-nitrobenzylidene)-5-phenylpyrazolidin-3-on-1-azomethine imine 3{*1*}.** This compound was prepared from **1** (0.843 g, 3 mmol) and 4-nitrobenzaldehyde **2**{*1*} (0.544 g, 3.6 mmol).

(1*Z*,4*R,5*R**)-4-Benzoylamino-1-benzylidene-5-phenylpyrazolidin-3-on-1-azomethine imine 3{*2*}.** The compound was prepared from **1** (0.843 g, 3 mmol) and benzaldehyde **2**{*2*} (382 mg, 3.6 mmol).

(1*Z*,4*R,5*R**)-4-Benzoylamino-1-(4-methoxybenzylidene)-5-phenyl-pyrazolidin-3-on-1-azomethine imine 3{*3*}.** This compound was prepared from **1** (0.843 g, 3 mmol) and 4-methoxybenzaldehyde **2**{*3*} (0.490 g, 3.6 mmol).

(1*Z*,4*R,5*R**)-4-Benzoylamino-1-(2,4-dichlorobenzylidene)-5-phenyl-pyrazolidin-3-on-1-azomethine imine 3{*4*}.** This compound was prepared from **1** (0.843 g, 3 mmol) and 2,4-dichlorobenzaldehyde **2**{*4*} (0.630 g, 3.6 mmol). Yield: 1.050 g (80%) of a white solid. mp: 226−230 °C. IR (KBr): ν_{max} 3274 (NH); 1675, 1655 ν(C═O) cm^{-1}. ^1H NMR (DMSO-d_6): δ 4.73 (3H, dd, J = 5.9, 7.6 Hz, 4-H), 6.00 (1H, dd, J = 1.1, 5.9 Hz, 5-H), 7.37 (1H, br s, 1′-H), 7.51 (8H, m, 8H of Ph), 7.70 (1H, dd, J = 2.3, 8.7 Hz, 5′-H of $C_6H_3Cl_2$), 7.79 (1H, d, J = 2.3 Hz, 3′-H of $C_6H_3Cl_2$), 7.87 (2H, m, 2H of Ph), 9.22 (1H, d, J = 8.7 Hz, 6′-H of $C_6H_3Cl_2$), 9.24 (1H, d, J = 7.6 Hz, NH). Anal. Calcd for $C_{23}H_{17}Cl_2N_3O_2$ (438.31): C, 63.03; H, 3.91; N, 9.59. Found: C, 62.99; H, 4.01; N, 9.52.

(1*Z*,4*R,5*R**)-4-Benzoylamino-5-phenyl-1-(2,4,6-trimethylbenzylidene)pyrazolidin-3-on-1-azomethine imine 3{*5*}.** This compound was prepared from **1** (0.843 g, 3 mmol) and 2,4,6-trimethylbenzaldehyde **2**{*5*} (0.533 g, 3.6 mmol).

(1*Z*,4*R,5*R**)-4-Benzoylamino-1-(2,6-dichlorobenzylidene)-5-phenylpyrazolidin-3-on-1-azomethine imine 3{*6*}.** This compound was prepared from **1** (0.843 g, 3 mmol) and 2,6-dichlorobenzaldehyde **2**{*6*} (0.630 g, 3.6 mmol).

General Procedure for the Preparation of 1-Substituted Alkyl (1*S,2*S**,3*R**,5*R**,6*R**)-3-Aryl-6-benzoylamino-1-hydroxy-7-oxo-5-phenylhexahydropyrazolo[1,2-*a*]pyrazole-2-carboxylates 5 and Their Minor (1*R**,2*S**,3*R**,5*R**,6*R**)-Epimers 6.** The MiniBlock was equipped with 12 fritted vessels and the frits were wetted with MeOH (0.5 mL each). Azomethine imines **3**{*1*−*4*} (3 × 2 mmol) were added, followed by addition of MeOH (12 × 10 mL), β-keto esters **4**{*1*−*3*} (4 × 2.4 mmol), and Et_3N (12 × 0.248 mL, 12 × 2.4 mmol). The MiniBlock was closed, and the reaction mixtures were vortexed at RT for 24 h. The MiniBlock was opened, and the precipitates were collected by filtration, washed with Et_2O (12 × 10 mL), and dried in vacuo (RT, 0.1 Torr) to give cycloadducts **5/6**. In the same manner, cycloadditions of dipoles **3**{*1*−*4*} were also performed with β-keto esters **4**{*4*−*6*} and **4**{*7*−*9*}. Compounds **5**{*3*; *5*}, **5/6**{*2*−*4*; *6*}, **5**{*1*; *8*}, and **5**{*4*; *9*} were additionally purified by FC (silica gel, ethyl acetate−hexanes). Fractions containing the product were combined and evaporated in vacuo to give pure compounds **5**{*3*; *5*}, **5/6**{*2*−*4*; *6*}, **5**{*1*; *8*}, and **5**{*4*; *9*}. Compounds **5/6**{*1*,*2*; *1*}, **5/6**{*1*−*3*; *2*}, **5/6**{*1*−*4*; *3*}, **5**{*1*,*2*; *4*}, **5/6**{*1*−*4*; *5*−*7*} were prepared in this manner.

Experimental data for compounds **5/6** are given in Table 1. Analytical and spectral data for compounds **5/6** are given in Supporting Information (Tables 1 and 2).

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Supporting Information Available. Analytical and spectral data for compounds **5/6**, NMR structure determination data for compounds **5/6**, and X-ray data for compound **5**{*2*; *4*}. This material is available free of charge via the Internet at http://pubs.acs.org.

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