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Synthesis of functionalized pyrazole derivatives by regioselective [3 + 2] cycloadditions of *N*-Boc-α-amino acid-derived ynones

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Abstract: [3 + 2] cycloadditions of ynones derived from glycine and (*S*)-alanine and some other dipolarophiles with azomethine imines, nitrile oxides, diazoacetate, and azidoacetate were studied. The dipolarophiles were obtained from α-amino acids, either by the reduction of the carboxy function with ethynylmagnesium bromide or by propiolation of the amino function. Cu-catalyzed cycloadditions of ynones to azomethine imines were regioselective and gave the expected cycloadducts as inseparable mixtures of diastereomers. In some instances, further oxidative hydrolytic ring-opening took place to afford 3,3-dimethyl-3-(1*H*-pyrazol-1-yl)propanoic acids. Acid-catalyzed cycloadditions of 3-butenone were also regioselective and provided mixtures of diastereomeric cycloadducts, which were separated by chromatography. In the reactions of title ynones with alkyl diazoacetates, *in situ*-formed benzonitrile oxides, and *tert*-butyl azidoacetate, all cycloadducts were obtained as single regioisomers. The structures of all novel compounds were established by nuclear magnetic resonance and X-ray diffraction.

Keywords: [3 + 2] cycloadditions; azomethine imines; heterocycles; pyrazolidinones; regioselectivity; stereoselectivity.

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1 Introduction

Various heterocyclic systems are important scaffolds that have found widespread use and application as reagents, building blocks, and ligands in synthetic chemistry, catalysis, and materials science [1]. In this context, pyrazoles are important heterocycles that are constituents of numerous synthetic products. Although they are only rarely found in natural products, the pyrazole core represents an important replacement for the naturally abundant pyrrole and imidazole residue in numerous synthetic bioactive compounds. Accordingly, pyrazole derivatives are used as active pharmaceutical ingredients, agrochemicals, catalysts, and materials [1–4]. Some examples of important pyrazole derivatives are depicted in Fig. 1.

Two classic routes toward pyrazole derivatives are based on cyclocondensation of hydrazine derivatives with 1,3-dicarbonyl compounds and their analogues or on [3 + 2] cycloadditions of diazoalkanes, nitrile imines, and azomethine imines to acetylenic and olefinic dipolarophiles. The latter approach is particularly useful for a stereoselective synthesis of (partially) saturated analogues, i.e. pyrazolines and pyrazolidines [1–4].

3-Pyrazolidinones are an important class of saturated heterocycles due to their applicability in industrial processes and biological activity. They have been used as dyes and photographic developers whereas their bioactivities range from antibacterial, analgesic, antipyretic, and anti-inflammatory to the inhibition of cyclooxygenase and lipoxygenase [5–9]. 3-Pyrazolidinones are commonly available by treatment of an α,β-unsaturated carboxylic acid derivative with hydrazine hydrate. The 1,2-unsubstituted compounds react with aromatic aldehydes to form the corresponding azomethine imines. [3 + 2] cycloadditions of these stable 1,3-dipoles provide elegant stereoselective access to bicyclic pyrazolidinones. Other reactions, such as reduction and ring transformation, have also been reported [5–11].

Recently, a portion of our research interest has been focused on the application of α-amino acid-derived ynones **4** as the key intermediates in the synthesis of vinylogous

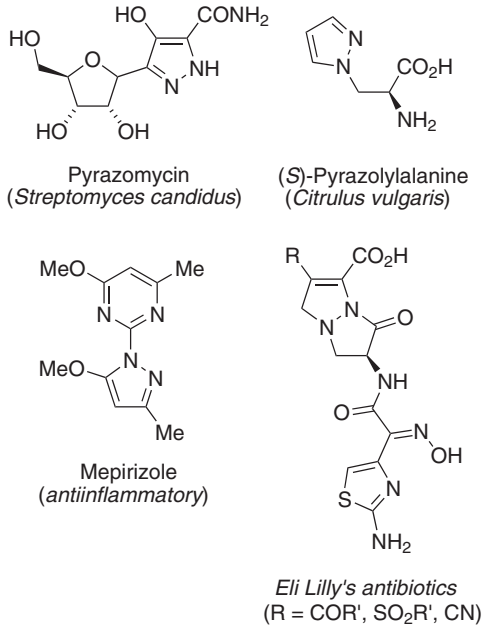


Fig. 1: Some examples of important pyrazole derivatives.

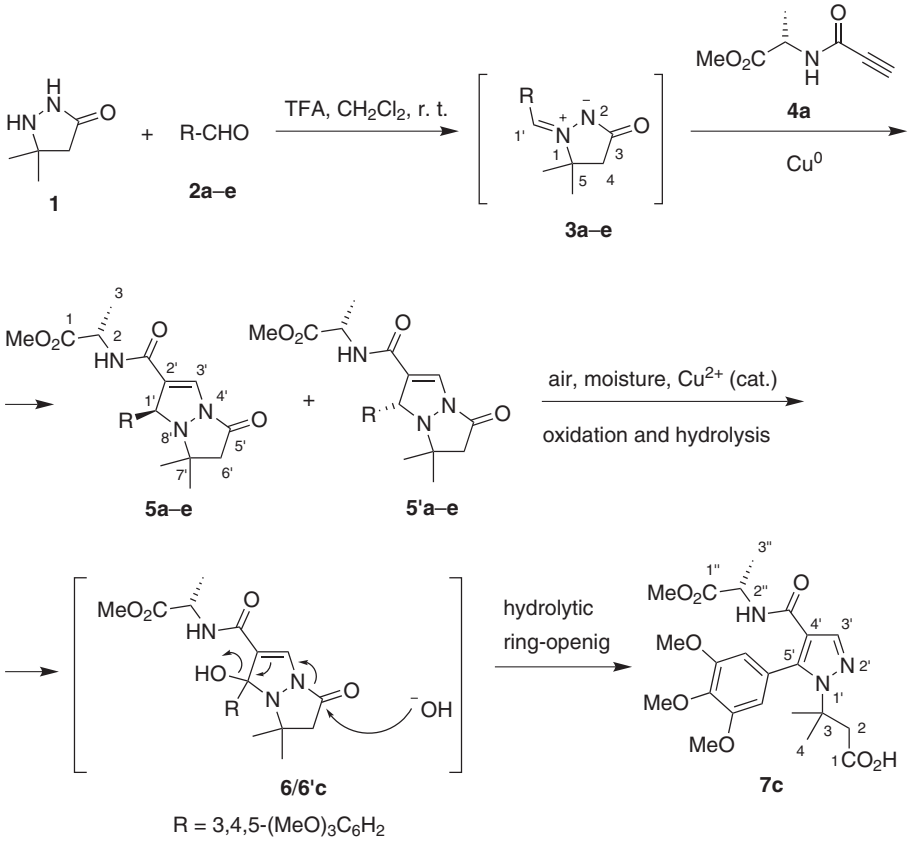
peptides [12], nonracemic 1-(heteroaryl)alkylamines [13], and bicyclic pyrazolidinones [14–17]. In extension, application of ynones **4** in [3 + 2] cycloadditions to azomethine imines, nitrile oxides, and other dipoles have been evaluated. Herein, we report the results of this study, which revealed the high regioselectivity of these reactions even for thermal, noncatalyzed cycloadditions.

2 Results and discussion

First, Cu^0-catalyzed cycloadditions of methyl propiolyl-L-alaninate (**4a**) to (*Z*)-1-arylmethylidene-5,5-dimethyl-3-oxopyrazolidin-1-ium-2-ides **3a–e** were studied. Ynone **4a** was prepared by acylation of methyl L-alaninate with propiolic acid following slightly modified literature procedure [18]. Azomethine imines **3a–d** [15, 19–21] and **3e** were formed *in situ* by acid-catalyzed treatment of 5,5-dimethylpyrazolidin-3-one (**1**) [22] with a slight excess of aldehydes **2a–e** in dichloromethane at room temperature for 3–24 h. This was followed by the addition of **4a** and copper powder to carry out cycloadditions, essentially under reaction conditions, which were optimized previously in closely related reactions [15]. Thus, treatment of the *in situ* prepared dipoles **3a–e** with ynone **4a** in the presence of copper powder as catalyst in dichloromethane at room temperature for 24 h, followed by purification by column chromatography (CC), produced the expected cycloadducts as mixtures of diastereomers **5a–e** and **5′a–e** in 27%–66% isolated yields. When the crude non-purified oily product **5c**/**5′c** was left to stand overnight in an open flask or when the time of the reaction was prolonged (5 days), **5c**/**5′c** was quantitatively converted into 3-(4,5-disubstituted-1*H*-pyrazol-1-yl)-3-methylbutanoic acid **7c**. On the other hand, cycloadducts **5**/**5′a**, **b**, **d**, **e** remained unchanged under the above conditions. The ring-opened product **7c** was also obtained in 44% yield upon prolonged treatment (5 days) of dipole **3c** with **4a** in the presence of copper powder and without strict exclusion of air and moisture followed by chromatographic workup. Oxidative transformation of cycloadduct **5**/**5′c** into the 3-pyrazolylbutanoic acid **7c** is explainable by Cu^{2+}-catalyzed aerobic oxidation at the benzylic position to give the 1-hydroxylated analogue **6**/**6′c** followed by hydrolytic ring-opening to furnish the carboxylic acid **7c**. Higher stability of cycloadducts **5**/**5′a**, **b**, **d**, **e** against oxidation is in agreement with activation of benzylic position by an electron-rich aryl group. Analogous oxidative ring-opening with bromine in methanol [23] and ceric ammonium nitrate [24, 25] have been reported previously (Scheme 1).

Acid-catalyzed cycloadditions of **3b**, **c** to but-3-en-2-one (**8**) were highly regioselective and furnished mixtures of the major *exo*-isomers **9a**, **b** and the minor *endo*-isomers **9′a**, **b**. Upon chromatographic separation, isomerically pure products **9a**, **9b**, **9′a**, and **9′b** were isolated in 17%–68% yields. Regioselectivity of cycloadditions to butenone **8** is explainable by electronic effects, i.e. by the protonation of the carbonyl group of **8**, which activates the electrophilic β-position for the reaction with the dipole **3** with the negative charge residing mostly on the nitrogen atom. The same regioselectivity has also been obtained in the reactions of closely related dipoles with α-trifluoromethylacrylates [26, 27]. The stereoselectivity of cycloadditions, on the other hand, is in line with the predominant *exo*-attack of **8** to the dipole **3**. However, because the cycloadditions of azomethine imines to olefins are usually *endo*-selective, the *exo*-selectivity is explainable by the steric hindrance caused by the two methyl groups at position 5 (Scheme 2).

Cycloadditions of alkyl diazoacetates **10a**, **b** to *tert*-butyl (*S*)-(3-oxopent-4-yn-2-yl)carbamate (**4b**), and *tert*-butyl (2-oxobut-3-yn-1-yl)carbamate (**4c**) [12, 14], but-1-yn-3-one (**4d**), and 1-phenylprop-2-yn-1-one (**4e**) were also highly regioselective. Reactions were performed in acetonitrile at room temperature to afford alkyl 5-acyl-1*H*-pyrazole-2-carboxylates **11a–f** as single regioisomers in 8%–80% yields. Cycloadditions of the nonracemic ynone **4b** to benzonitrile oxides were carried out by treatment of **4b** with hydroxamoyl chlorides **12a**, **b** [28] in the



		Yield (%)	
Reaction	**R**	**5/5'**[a]	**7**
3a+**4a**→**5a**	4-$O_2NC_6H_4$	66	-
3b+**4a**→**5b**	4-ClC_6H_4	48	-
3c+**4a**→**5c**→**7c**	3,4,5-$(MeO)_3C_6H_2$	60	44
3d+**4a**→**5d**	Ph	65	-
3e+**4a**→**5e**	1-Propyl	27	-

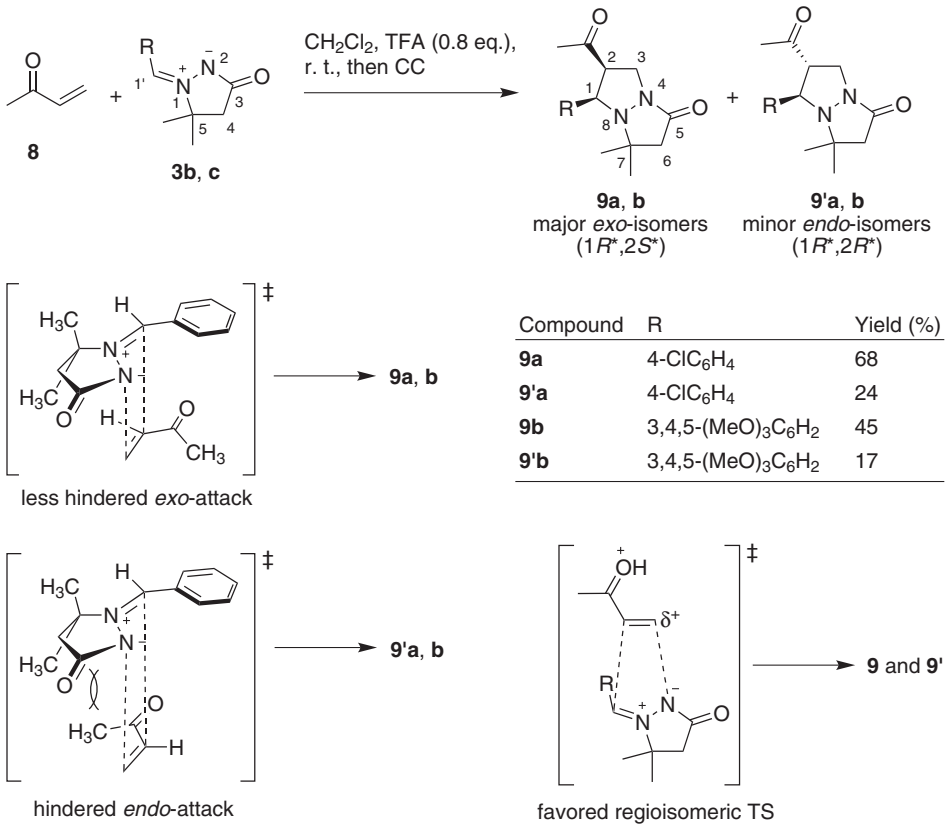
[a] Mixtures of diastereomers.

Scheme 1: Cu-catalyzed [3 + 2] cycloadditions of azomethine imines **3a–e** to ynone **4a**.

presence of triethylamine in anhydrous dichloromethane at room temperature to afford the racemic cycloadducts **13a**, **b** in moderate yields. Most probably, this undesired epimerization was induced by the presence of a base. Quite expectedly, CuI-catalyzed cycloaddition of *tert*-butyl azidoacetate (**14**) to the ynone **4b** was regioselective to furnish the nonracemic triazole derivative **15** in 38% yield (Scheme 3).

The structures of all novel compounds **5**/**5′a–e**, **7c**, **9a**, **9′a**, **9b**, **9′b**, **11c–f**, **13a**, **b**, and **15** were determined by spectroscopic methods [infrared spectroscopy (IR), ^{1}H and ^{13}C nuclear magnetic resonance (NMR), and high resolution mass spectrometry (HRMS)] and elemental analyses for C, H, and N. Novel compounds **5**/**5′a–e**, **9b**, **11c**, **e**, and **13b** were not obtained in analytically pure form. Their identities were confirmed by ^{13}C NMR and HRMS. Compounds **7c**, **9a**, **9′a**, **9b**, **9′b**, **11a–f**, **13a**, **b**, and **15** were obtained and characterized as single components, whereas compounds **5**/**5′a–e** were obtained as mixtures of diastereomers and were characterized as such.

The structure, regiochemistry, and configuration of cycloadducts **5**, **9**, **9′**, **11**, **13**, and **15** were established by NMR (Fig. 2). For the bicyclic pyrazolidinones **5**/**5′a–e**, the structure assignment was based primarily on the correlation of their ^{1}H NMR data with the literature data for closely related compounds [8, 14–17]. Thus, the δ chemical



Compound	R	Yield (%)
9a	4-ClC_6H_4	68
9'a	4-ClC_6H_4	24
9b	3,4,5-$(MeO)_3C_6H_2$	45
9'b	3,4,5-$(MeO)_3C_6H_2$	17

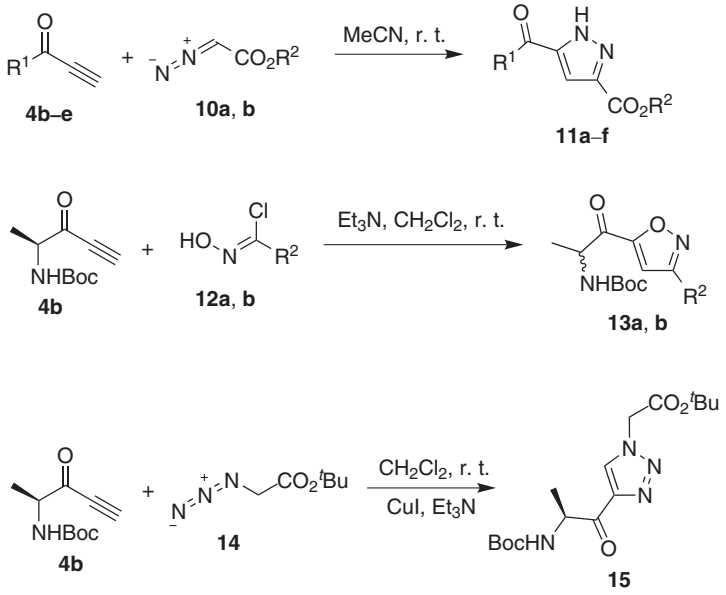
Scheme 2: [3+2] cycloadditions of azomethine imines **3b, c** to 3-buten-2-one (**8**).

shifts for 1′-H and 3′-H as well as characteristic coupling constant, $^4J_{1'H-3'H} \sim 1.5$ Hz, were in clear agreement with the proposed structures **5**/**5′**. Similarly, the regiochemistry of cycloadducts **9** and **9′** was determined on the basis of δ chemical shift for the 3-CH_2 protons, $\delta \sim 3.7$–4 ppm, which were characteristic for the NCH_2 moiety. On the other hand, unambiguous determination of the relative configuration of the *exo*-isomers **9** and the *endo*-isomers **9′** was not possible because of the similarity of the respective vicinal coupling constants, $^3J_{1H-2H} = 8.8$ and 8.7 Hz. Nevertheless, the configuration of compounds **9** and **9′** were established by combination of X-ray diffraction data for **9a** (see also Fig. 4) and correlation of characteristic δ chemical shifts and vicinal coupling constants, $^3J_{1H-2H}$ (Fig. 2). The regiochemistry of the pyrazoles **11**, isoxazoles **13**, and 1,2,3-triazole **15** were determined on the basis of chemical shifts δ for the aromatic protons 4-H and 5-H, which were in agreement with the literature data for these heterocyclic systems [1–4, 29–31].

The crystal and molecular structures of compounds **7c**, **9a**, and **13a** were determined by single-crystal X-ray diffraction. Drawings of the molecular structures of compounds **7c**, **9a**, and **13a** in the crystal are depicted in Figs. 3–5, respectively.

3 Conclusion

Ynones **4a–c**, derived from α-amino acid derivatives by the reduction of corresponding Weinreb amides or by propiolation of amino esters, undergo [3+2] cycloaddition reactions with various 1,3-dipoles, such as azomethine imines, nitrile oxides, diazoacetates, and azidoacetates. Cycloadditions to all above-mentioned 1,3-dipoles proceeded regioselectively under mild conditions. In contrast to analogous reactions of achiral azomethine imines **3a–d** with nonracemic ynones **4b**, **c** that gave mixtures of nonracemic diastereomers separable by chromatography [14, 17], the Cu-catalyzed cycloadditions of achiral azomethine imines **3a–d** to the nonracemic methyl propiolyl-L-alaninate (**4a**) gave the expected cycloadducts **5**/**5′a–e** as inseparable mixtures of diastereomers. Cycloadduct **5**/**5′c** bearing electron-rich 3,4,5-trimethoxyphenyl group at position 1 underwent further oxidative hydrolytic ring-opening to afford the respective 3,3-dimethyl-3-(4,5-disubstituted 1*H*-pyrazol-1-yl)propanoic acid **7c**. On the other hand, mixtures of diastereomeric cycloadducts obtained upon acid-catalyzed *endo*-selective cycloadditions of **3b**, **c** to 3-buten-2-one (**8**) were separable and all cycloadducts, **9a**, **9′a**, **9b**, and **9′b**, were obtained in isomerically pure



Compound	R^1	R^2	Yield (%)
11a	$CH(CH_3)NHBoc$	Et	80
11b	CH_2NHBoc	Et	8
11c	$CH(CH_3)NHBoc$	Bn	51
11d	CH_2NHBoc	Bn	36
11e	Me	Et	54
11f	Ph	Et	57
13a	/	C_6H_5	37
13b	/	2,6-$Cl_2C_6H_4$	30
15	/	/	38

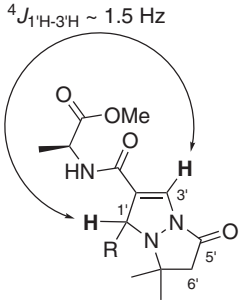
Scheme 3: [3 + 2] cycloadditions of ynones **4b–e** to diazoacetates **10a**, **b**, hydroxamoyl chlorides **12a**, **b**, and *tert*-butyl azidoacetate (**14**).

form. Reactions of title ynones **4b**, **c** with alkyl diazoacetates **10a**, **b**, hydroxamoyl chlorides **12a**, **b**, and *tert*-butyl azidoacetate (**14**) gave the expected cycloadducts as single regioisomers. In summary, the present study shows that the [3 + 2] cycloadditions of α-amino acid-derived ynones **4a–c** to various 1,3-dipoles provide an easy entry toward the preparation of nonracemic heterocyclic compounds functionalized with an α-amino acid and/or α-amino ketone functionality under mild reaction conditions.

4 Experimental section

Melting points were determined on a Stanford Research Systems MPA100 OptiMelt automated melting point system. The NMR spectra were obtained on a Bruker Avance III UltraShield 500 plus at 500 MHz for ^{1}H and at 126 MHz for ^{13}C nucleus, respectively, using $CDCl_3$ and [D_6]DMSO as solvents with tetramethylsilane as the internal standard. Mass spectra were recorded on an Agilent 6224 Accurate Mass time of flight liquid chromatography/mass spectrometry spectrometer and IR spectra on a Bruker FTIR Alpha Platinum ATR spectrophotometer. Microanalyses were performed on a Perkin-Elmer CHN Analyzer 2400 II. Column chromatography and flash column chromatography (FC), was performed on silica gel (Fluka, silica gel 60, particle size 35–70 µm). Medium-performance liquid chromatography was done on a Büchi Flash Chromatography System (Büchi Fraction Collector C-660, Büchi Pump Module C-605, Büchi Control Unit C-620) on silica gel (LiChroprep® Si 60, 15–25 µm), column dimensions: 23 × 460 mm, backpressure: 10 bar, detection: UV (254 nm).

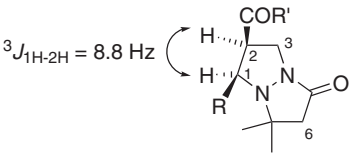
Aldehydes **2a–e**, trifluoroacetic acid, copper powder, methyl L-alaninate hydrochloride, triethylamine, 4-methylmorpholine, but-1-yn-3-one (**4d**), 1-phenylprop-2-yn-1-one (**4e**), 3-buten-2-one (**8**), ethyl diazoacetate (**10a**), benzyl diazoacetate (**10b**), and *tert*-butyl azidoacetate (**14**) are commercially available. 5,5-Dimethylpyrazolidin-3-one (**1**) [22], azomethine imines **3a**, **c** [19] and **3b**, **d** [20, 21], methyl *N*-propioloyl-L-alaninate (**4a**) [18], *tert*-butyl (*S*)-(3-oxopent-4-yn-2-yl)carbamate (**4b**) and *tert*-butyl



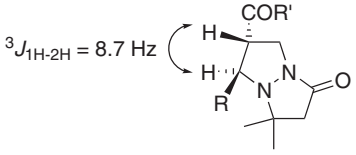
5a–e/5'a–e

Compound	δ (ppm) 1'-H	3'-H	$^4J_{1'H\text{-}3'H}$ (Hz)
5a/5'a	5.72/5.73	7.90/7.98	1.6
5b/5'b	5.55/5.57	7.81/7.88	1.6
5c/5'c	5.50/5.55	7.72/7.78	1.5
5d/5'd	5.52/5.55	7.78/7.85	1.6
5e/5'e	[a]	7.64/7.68	1.4

[a] Multiplet.



exo-isomers **9a**, **b**



endo-isomers **9'a**, **b**

Compound	δ (ppm) 1-H	2-H	3-Ha	3-Hb	6-Ha	6-Hb	$^4J_{1H\text{-}2H}$ (Hz)
9a	4.12	3.44	~3.7[b]	~3.9[a]	2.51	2.56	8.8
9'a	4.06	3.50	3.61	3.90	2.48	2.63	8.7
9b	4.28	3.74[a]	3.78[a]	3.85[a]	2.53	2.59	8.8
9'b	4.22	3.72	3.60	3.89	2.49	2.67	8.7

[a] Multiplet. [b] Overlapped by other signals.

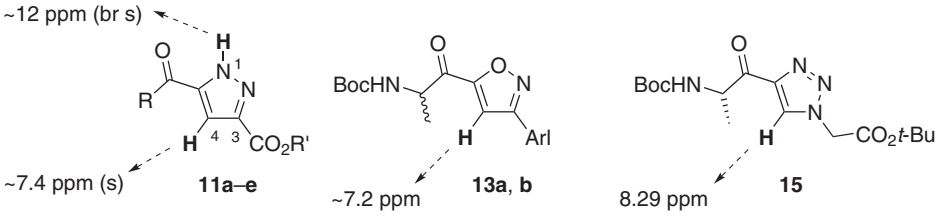


Fig. 2: Determination of structures of compounds **5**/**5′**, **9**, **9′**, **11**, **13**, and **15** by NMR.

(2-oxobut-3-yn-1-yl)carbamate (**4c**) [12, 14], and hydroxamoyl chlorides **12a**, **b** [28] were prepared according to the literature procedures.

4.1 Methyl *N*-propioloyl-L-alaninate (4a) [18]

Compound **4a** was prepared by propiolation of methyl L-alaninate following slightly modified literature procedure [18]. *N*,*N*′-Dicyclohexylcarbodiimide (4.12 g, 20 mmol) was added to a stirred cold (0°C, ice bath) solution of propiolic acid (1.40 g, 20 mmol) in anhydrous dichloromethane (40 mL) and the mixture was stirred at 0°C for 20 min. Then, methyl L-alaninate hydrochloride (1.40 g, 10 mmol) and 4-methylmorpholine (1.10 mL, 10 mmol) were added and the reaction mixture was stirred, first at 0°C for 1 h and then at room temperature for 24 h. *N*,*N*′-Dicyclohexylurea, which precipitated from the reaction mixture, was collected by filtration and washed with anhydrous dichloromethane (2×10 mL). The combined filtrate was evaporated *in vacuo* and the residue was purified by CC (dichloromethane). Fractions containing the product were combined and evaporated *in vacuo*. The residue was triturated with diethyl ether (40 mL), the precipitated *N*,*N*′-dicyclohexylurea was removed by filtration and washed with diethyl ether (2×5 mL), and

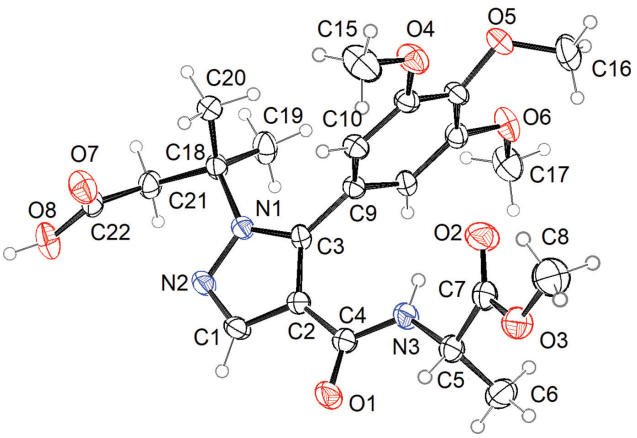


Fig. 3: ORTEP-III representation of one of the crystallographically independent molecules of compound **7c** in the crystal. Ellipsoids are plotted at the 30% probability level, H atoms as spheres with arbitrary radii.

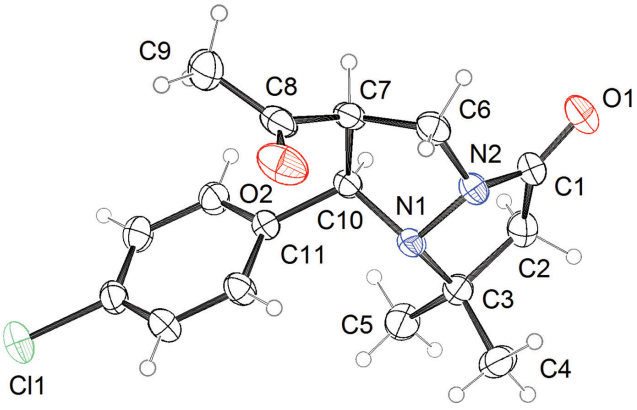


Fig. 4: ORTEP-III representation of the molecular structure of compound **9a** in the crystal. Ellipsoids are plotted at the 30% probability level, H atoms as spheres with arbitrary radii.

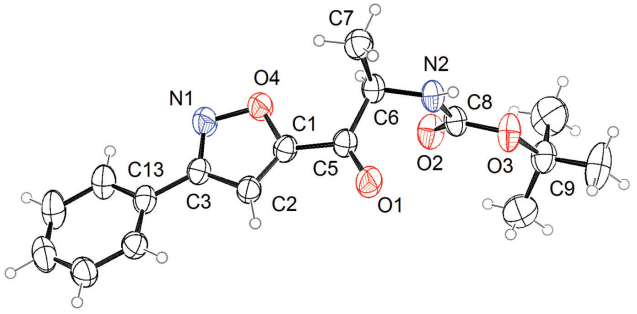


Fig. 5: ORTEP-III representation of the molecular structure of compound **13a** in the crystal. Ellipsoids are plotted at the 30% probability level, H atoms as spheres with arbitrary radii.

the combined filtrate was evaporated *in vacuo* to give **4a**. Yield: 496 mg (32%) of yellowish oil. Spectral and physical data for **4a** were in agreement with the literature data [18].

4.2 Synthesis of methyl (2*S*,1′*S*)-[7,7-dimethyl-1-substituted-5-oxo-6,7-dihydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-2-carbonyl)alaninates 5a–e and their (2*S*,1′*R*)-isomers 5′a–e

Aldehydes **2a–e** (1.3 mmol) and trifluoroacetic acid (one drop) were added subsequently to a stirred mixture of the pyrazolidinone **1** (114 mg, 1 mmol) and anhydrous dichloromethane (5 mL) and stirring at room temperature was continued for 3–24 h. Then, ynone **4a** (155 mg, 1 mmol) was added and the mixture was stirred at room temperature for 24 h. Volatile components were evaporated *in vacuo* and the residue was purified by CC (EtOAc-hexanes, 1:1). Fractions containing the product were combined and evaporated *in vacuo* to afford mixtures of diastereomers **5a–e** and **5′a–e**. The following compounds were prepared in this manner.

4.2.1 Methyl (2*S*,1′*S*)-[7,7-dimethyl-1-(4-nitrophenyl)-5-oxo-6,7-dihydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-2-carbonyl]alaninate (5a) and its (2*S*,1′*R*)-isomer 5′a

Prepared from **1** (84 mg, 0.74 mmol) and **2a** (150 mg, 0.98 mmol), 24 h; then **4a** (153 mg, 0.99 mmol) and copper powder (33 mg). Yield: 196 mg (66%) of a yellow resin. – IR (ATR): ν = 3325, 2928, 1747, 1702, 1643, 1519, 1343, 1213, 833 cm^{-1}. – ^{1}H NMR (500 MHz, [D$_6$]DMSO]): δ = 1.09, 1.11, 1.16, and 1.17 (12H, 4s, 1:1:1:1, 4×7′-CH$_3$), 1.24 and 1.26 (6H, 2d, 1:1, J = 7.5, 7.4 Hz, 2×CHC*H*$_3$), 2.39 and 2.40 (2H, 2d, 1:1, J = 15.7 Hz, 2×6′-H$_a$), 2.857 and 2.861 (2H, 2d, 1:1, J = 15.7 Hz, 2×6′-H$_b$), 3.51 and 3.58, (6H, 2s, 1:1, 2×CO$_2$CH$_3$), 4.14 and 4.24 (2H, 2p, 1:1, J = 7.2, 6.9 Hz, 2×C*H*CH$_3$), 5.72 and 5.73 (2H, 2d, 1:1, J = 1.6 Hz, 2×1′-H), 7.68–7.71 and 8.17–8.22 (8H, 2m, 8H of Arl), 7.90 and 7.98 (2H, 2d, 1:1, J = 1.5 Hz, 2×3′-H), 8.24 and 8.26 (2H, 2d, 1:1, J = 6.4, 6.8 Hz, 2×NH). – ^{13}C NMR (126 MHz, [D$_6$]DMSO]): δ = 16.6, 16.9, 18.0, 18.1, 24.01, 24.04, 47.6, 47.7, 48.0, 48.1, 51.7, 51.8, 63.59, 63.60, 64.9, 65.0, 118.3, 118.4, 123.2, 123.3, 126.9, 127.1, 129.0, 129.1, 146.70, 146.71, 150.65, 150.72, 162.4, 167.4, 167.6, 172.9, 173.1. – HRMS ((+)-ESI): m/z = 403.161 (calcd. 403.1612 for C$_{19}$H$_{23}$N$_4$O$_6$, [M+H]$^+$).

4.2.2 Methyl (2*S*,1′*S*)-[7,7-dimethyl-1-(4-chlorophenyl)-5-oxo-6,7-dihydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-2-carbonyl]alaninate (5b) and its (2*S*,1′*R*)-isomer 5′b

Prepared from **1** (64 mg, 0.56 mmol) and **2b** (85 mg, 0.60 mmol), 24 h; then **4a** (85 mg, 0.55 mmol) and copper powder (33 mg). Yield: 104 mg (48%) of a yellow resin.

– IR (ATR): ν = 3325, 2929, 1733, 1626, 1542, 1450, 1203, 1089, 837, 642 cm^{-1}. – ^{1}H NMR (500 MHz, [D$_6$]DMSO]): δ = 1.08, 1.10, 1.13 and 1.14 (12H, 4s, 1:1:1:1, 4 × 7′-CH$_3$), 1.24 and 1.25 (6H, 2d, 1:1, J = 7.3 Hz, 2 × CHC*H*$_3$), 2.36 and 2.37 (2H, 2d, 1:1, J = 15.6 Hz, 2 × 6′-H$_a$), 2.83 and 2.84 (2H, 2d, 1:1, J = 15.7, 15.8 Hz, 2 × 6′-H$_b$), 3.53 and 3.57 (6H, 2s, 1:1, 2 × CO$_2$CH$_3$), 4.15 and 4.23 (2H, 2p, 1:1, J = 7.2, 7.3 Hz, 2 × C*H*CH$_3$), 5.55 and 5.57 (2H, 2d, 1:1, J = 1.7, 1.6 Hz, 2 × 1′-H), 7.35–7.42 (8H, 2m, 8H of Arl), 7.81 and 7.88 (2H, 2d, 1:1, J = 1.4, 1.5 Hz, 2 × 3′-H), 8.18 and 8.20 (2H, 2d, 1:1, J = 6.3, 6.9 Hz, 2 × NH). – ^{13}C NMR (126 MHz, [D$_6$]DMSO]): δ = 16.6, 16.9, 18.0, 18.1, 24.09, 24.12, 47.5, 47.6, 48.1, 48.2, 51.7, 51.8, 63.45, 63.49, 64.7, 64.8, 118.9, 119.0, 126.4, 126.7, 127.96, 127.99, 129.5, 129.6, 131.70, 131.72, 142.2, 142.3, 162.5, 167.3, 167.4, 172.9, 173.1. – HRMS ((+)-ESI): m/z = 392.1371 (calcd. 392.1372 for C$_{19}$H$_{23}$ClN$_3$O$_4$, [M + H]$^+$).

4.2.3 Methyl (2*S*,1′*S*)-[7,7-dimethyl-1-(3,4,5-trimethoxyphenyl)-5-oxo-6,7-dihydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-2-carbonyl]alaninate (5c) and its (2*S*,1′*R*)-isomer 5′c

Prepared from **1** (64 mg, 0.56 mmol) and **2c** (117 mg, 0.60 mmol), 16 h; then **4a** (80 mg, 0.52 mmol) and copper powder (20 mg), 24 h. Yield: 139 mg (60%) of a yellow residue as a mixture of diastereomers. – IR (ATR): ν = 3339, 2939, 1733, 1710, 1638, 1592, 1421, 1230, 1121, 1005, 767, 732 cm^{-1}. – ^{1}H NMR (500 MHz, [D$_6$]DMSO]): δ = 1.13, 1.14, 1.16, and 1.20 (12H, 4s, 1:1:1:1, 4 × 7′-CH$_3$), 1.26 and 1.27 (6H, 2d, 1:1, J = 7.0, 7.1 Hz, 2 × C*H*CH$_3$), 2.35 and 2.36 (2H, 2d, 1:1, J = 15.6 Hz, 2 × 6′-H$_a$), 2.837 and 2.843 (2H, 2d, 1:1, J = 15.7, 15.6 Hz, 2 × 6′-H$_b$), 3.54, 3.58, 3.639, 3.641, 3.74 and 3.75 (24H, 6s, 1:1:1:1:2:2, 2 × CO$_2$CH$_3$ and 6 × OCH$_3$), 4.21 and 4.27 (2H, 2p, 1:1, J = 7.3 Hz, 2 × C*H*CH$_3$), 5.50 and 5.53 (2H, 2d, 1:1, J = 1.3, 1.2 Hz, 2 × 1′-H), 6.69 and 6.70 (4H, 2s, 1:1, 4H of Arl), 7.72 and 7.78 (2H, 2d, 1:1, J = 1.5 Hz, 2 × 3′-H), 8.16 and 8.23 (2H, 2d, 1:1, J = 7.0, 7.3 Hz, 2 × NH). – ^{13}C NMR (126 MHz, [D$_6$]DMSO]): δ = 16.7, 16.8, 17.9, 18.0, 24.19, 24.22, 47.5, 47.6, 48.15, 48.22, 51.7, 51.8, 55.7, 55.8, 59.86, 59.87, 64.1, 64.3, 64.8, 64.9, 104.7, 104.9, 118.9, 119.1, 126.4, 126.8, 136.5, 136.6, 138.5, 138.7, 152.56, 152.60, 162.8, 162.9, 167.5, 167.8, 173.08, 173.10. – HRMS ((+)-ESI): m/z = 448.2079 (calcd. 448.2078 for C$_{22}$H$_{30}$N$_3$O$_7$, [M + H]$^+$).

4.2.4 Methyl (2*S*,1′*S*)-[7,7-dimethyl-1-phenyl-5-oxo-6,7-dihydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-2-carbonyl]alaninate (5d) and its (2*S*,1′*R*)-isomer 5′d

Prepared from **1** (62 mg, 0.54 mmol) and **2d** (56 µL, 0.55 mmol), 3 h; then **4a** (93 mg, 0.60 mmol) and copper powder (20 mg). Yield: 80 mg (47%) of a yellow resin. – IR (ATR): ν = 3325, 2976, 2933, 1733, 1710, 1631, 1537, 1206, 1047, 698 cm^{-1}. – ^{1}H NMR (500 MHz, [D$_6$]DMSO]): δ = 1.09, 1.11, 1.13 and 1.14 (12H, 4s, 1:1:1:1, 4 × 7′-CH$_3$), 1.236 and 1.242 (6H, 2d, 1:1, J = 7.3 Hz, 2 × CHC*H*$_3$), 2.35 and 2.36 (2H, 2d, 1:1, J = 15.6 Hz, 2 × 6′-H$_a$), 2.82 and 2.83 (2H, 2d, 1:1, J = 15.6 Hz, 2 × 6′-H$_b$), 3.52 and 3.57 (6H, 2s, 1:1, 2 × CO$_2$CH$_3$), 4.15 and 4.23 (2H, 2p, 1:1, J = 7.2, 7.3 Hz, 2 × C*H*CH$_3$), 5.52 and 5.55 (2H, 2br s, 1:1, 2 × 1′-H), 7.21–7.38 (10H, m, 2 × Ph), 7.78 and 7.85 (2H, 2d, 1:1, J = 1.6, 1.5 Hz, 2 × 3′-H), 8.157 and 8.162 (2H, 2d, 1:1, J = 6.9, 7.3 Hz, 2 × NH). – ^{13}C NMR (126 MHz, [D$_6$]DMSO]): δ = 16.7, 16.9, 18.0, 18.1, 24.1, 24.2, 47.5, 47.6, 48.1, 48.2, 51.71, 51.74, 64.1, 64.2, 64.77, 64.83, 119.2, 119.3, 126.3, 126.7, 127.10, 127.13, 127.6, 127.7, 127.99, 128.01, 143.05, 143.13, 162.7, 167.5, 167.6, 173.0, 173.1. – HRMS ((+)-ESI): m/z = 358.1766 (calcd. 358.1761 for C$_{19}$H$_{24}$N$_3$O$_4$, [M + H]$^+$).

4.2.5 Methyl (2*S*,1′*S*)-[7,7-dimethyl-1-propyl-5-oxo-6,7-dihydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-2-carbonyl]alaninate (5e) and its (2*S*,1′*R*)-isomer 5′e

Prepared from **1** (120 mg, 1.05 mmol) and **2e** (108 µL, 1.2 mmol), 23 h; then **4a** (175 mg, 1.1 mmol) and copper powder (40 mg). Yield: 93 mg (27%) of a yellow resin. – IR (ATR): ν = 3324, 2929, 1732, 1625, 1554, 1536, 1206, 1162, 1121, 892, 641 cm^{-1}. – ^{1}H NMR (500 MHz, [D$_6$]DMSO]): δ = 0.866 and 0.869 (6H, 2d, 1:1, J = 7.2, 7.3 Hz, 2 × CH$_2$CH$_2$C*H*$_3$); 0.94, 0.95, and 1.23 (12H, 3s, 1:1:2, 4 × 7′-CH$_3$), 0.98–1.08 and 1.41–1.49 (8H, 2m, 2 × C*H*$_2$C*H*$_2$CH$_3$), 1.30 (6H, br d, J = 7.4 Hz, 2 × CHC*H*$_3$), 2.27 and 2.28 (2H, 2d, 1:1, J = 15.4 Hz, 2 × 6′-H$_a$), 2.75–2.80 (2H, m, 2 × 6′-H$_b$), 3.617 and 3.621 (6H, 2s, 1:1, 2 × CO$_2$CH$_3$), 4.27–4.34 (2H, m, 2 × C*H*CH$_3$), 4.39–4.42 (2H, m, 2 × 1′-H), 7.64 and 7.68 (2H, 2d, 1:1, J = 1.4 Hz, 2 × 3′-H), 8.18 and 8.19 (2H, 2d, 1:1, J = 7.1, 7.2 Hz, 2 × NH). – ^{13}C NMR (126 MHz, [D$_6$]DMSO]): δ = 13.98, 14.01, 16.7, 17.5, 17.56, 17.60, 17.63, 24.19, 24.21, 37.79, 37.81, 47.5, 47.6, 47.7, 47.79, 47.82, 51.8, 60.4, 60.5, 64.96, 64.99, 118.8, 127.5, 127.6, 163.0, 163.1, 169.36, 169.41, 173.1, 173.2. – HRMS ((+)-ESI): m/z = 324.1921 (calcd. 324.1918 for C$_{16}$H$_{26}$N$_3$O$_4$, [M + H]$^+$).

4.3 Synthesis of (*S*)-3-{4-[(1-methoxy-1-oxopropan-2-yl)carbamoyl]-5-(3,4,5-trimethoxyphenyl)-1*H*-pyrazol-1-yl}-3-methylbutanoic acid (7c)

Aldehyde **2c** (1.3 mmol) and trifluoroacetic acid (one drop) were added to a stirred solution of pyrazolidinone **1** (114 mg, 1 mmol) in anhydrous dichloromethane (5 mL) and

the mixture was stirred at room temperature for 24 h. Then, ynone **4a** (155 mg, 1 mmol) was added and stirring at room temperature was continued for 120 h. Volatile components were evaporated *in vacuo* and the residue was purified by FC (EtOAc-hexanes, 1:1). Fractions containing the product were combined and evaporated *in vacuo* to afford a mixture of **5**/**5′c** and **7c**, which was separated by medium-performance liquid chromatography (EtOAc). Fractions containing the product were combined and evaporated *in vacuo* to furnish the pure carboxylic acid **7c**. Yield: 408 mg (44%) of white solid. M. p. 144°C–145°C. – $[\alpha]_D^{22} = +25$ ($c = 0.47$, CH_2Cl_2). – IR (ATR): $\nu = 3396$, 2945, 1734, 1624, 1543, 1412, 1240, 1123, 1000, 848, 632 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): $\delta = 1.14$ (3H, d, $J = 7.1$ Hz, CH_3), 1.55 (6H, s, $2 \times CH_3$), 3.00 (1H, d, $J = 15.3$ Hz, 2-H_a), 3.04 (1H, d, $J = 15.3$ Hz, 2-H_b), 3.63, 3.86, 3.90 and 3.94 (12H, 4s, 1:1:1:1, $4 \times OCH_3$), 4.52 (1H, p, $J = 7.1$ Hz, 2″-H), 5.74 (1H, d, $J = 7.2$ Hz, NH), 6.66 and 6.71 (2H, 2d, 1:1 $J = 1.9$, 1.8 Hz, 2H of Arl), 8.05 (1H, s, 3′-H), 11.44 (1H, br s, CO_2H). – ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 18.6$, 29.5, 29.6, 47.9, 48.1, 52.4, 56.59, 56.64, 61.3, 63.5, 107.8, 108.2, 118.4, 125.6, 139.3, 139.7, 141.6, 154.0, 154.1, 162.0, 172.5, 172.9. HRMS ((+)-ESI): $m/z = 464.2018$ (calcd. 464.2027 for $C_{22}H_{30}N_3O_8$, $[M + H]^+$) – $C_{22}H_{29}N_3O_8$: calcd. C 57.01, H 6.31, N 9.07; found C 57.13, H 7.00, N 9.13.

4.4 Synthesis of (1*R**,2*S**)-2-acetyl-1-aryl-7,7-dimethyltetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazol-5-ones 9a, b and their (1*R**,2*R**)-epimers 9′a, b

But-1-en-3-one (**8**) (108 µL, 1.3 mmol) and trifluoroacetic acid (61 µL, 0.8 mmol) were added to a stirred solution of azomethine imine **3** (1 mmol) in anhydrous dichloromethane (5 mL) and the mixture was stirred at room temperature for 5 days. Volatile components were evaporated *in vacuo* and the residue was purified by CC. First, isomer **9** was eluted with EtOAc-hexanes = 2:1, then the mobile phase was changed to EtOAc to elute the isomer **9′**. Fractions containing the products were combined and evaporated *in vacuo* to afford **9a**, **b** and their epimers **9′a**, **b**. The following compounds were prepared in this manner:

4.4.1 (1*R**,2*S**)-2-Acetyl-7,7-dimethyl-1-(4-chlorophenyl)-tetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazol-5-one (9a) and its (1*R**,2*R**)-epimer 9′a

Prepared from dipole **3b** (166 mg, 0.70 mmol), butenone **8** (75 µL, 0.90 mmol) and trifluoroacetic acid (45 µL, 0.6 mmol).

4.4.2 (1*R**,2*S**)-2-Acetyl-7,7-dimethyl-1-(4-chlorophenyl)tetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazol-5-one (9a)

Yield: 55 mg (24%) of pale yellow solid. M. p. 148°C–154°C. – IR (ATR): $\nu = 2974$, 2947, 1705, 1491, 1368, 1333, 1228, 1159, 1087, 1012, 833, 718, 656 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): $\delta = 1.08$ and 1.15 (6H, 2s, 2×7-CH_3), 2.02 (3H, s, $COCH_3$), 2.51 (1H, d, $J = 16.8$ Hz, 6-H_a), 2.56 (1H, d, $J = 16.9$ Hz, 6-H_b), 3.44 (1H, ddd, $J = 10.0$, 8.8, 6.9 Hz, 2-H), 3.61 (1H, t, $J = 10.7$ Hz, 3-H_a), 3.90 (1H, dd, $J = 11.3$, 6.9 Hz, 3-H_b), 4.12 (1H, d, $J = 8.8$ Hz, 1-H), 7.32–7.35 (2H, m, 2H of Arl), 7.38–7.42 (2H, m, 2H of Arl). – ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 23.5$, 29.3, 30.4, 42.3, 46.3, 59.4, 63.3, 63.5, 129.1, 129.2, 134.1, 138.2, 171.0, 204.4. – HRMS ((+)-ESI): $m/z = 307.1206$ (calcd. 307.1208 for $C_{16}H_{20}ClN_2O_2$, $[M + H]^+$). – $C_{16}H_{19}ClN_2O_2 \cdot ¼H_2O$: calcd. C 61.73, H 6.31, N 9.00; found C 61.85, H 6.20, N 8.92.

4.4.3 (1*R**,2*R**)-2-Acetyl-7,7-dimethyl-1-(4-chlorophenyl)tetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazol-5-one (9′a)

Yield: 149 mg (68%) of pale yellow solid. M. p. 149°C–156°C. – IR (ATR): $\nu = 2931$, 1698, 1490, 1369, 1353, 1224, 1176, 1091, 1017, 846, 827, 705, 618 cm^{-1}.– ^1H NMR (500 MHz, $CDCl_3$): $\delta = 1.02$ and 1.21 (6H, 2s, 2×7-CH_3), 1.54 (3H, s, $COCH_3$), 2.48 (1H, d, $J = 16.7$ Hz, 6-H_a), 2.63 (1H, d, $J = 16.7$ Hz, 6-H_b), 3.70–3.77 (2H, m, 2-H and 3-H_a), 3.87–3.92 (1H, m, 3-H_b), 4.28 (1H, d, $J = 8.6$ Hz, 1-H), 7.29–7.34 (4H, m, 4H of Arl). – ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 23.2$, 29.4, 31.5, 41.5, 46.7, 58.5, 59.7, 64.3, 129.1, 129.7, 134.5, 135.5, 170.8, 205.6. – HRMS ((+)-ESI): $m/z = 307.1210$ (calcd. 307.1208 for $C_{16}H_{20}ClN_2O_2$, $[M + H]^+$). – $C_{16}H_{19}ClN_2O_2 \cdot ¼H_2O$: calcd. C 61.73, H 6.31, N 9.00; found C 62.03, H 6.22, N 9.00.

4.4.4 (1*R**,2*S**)-2-Acetyl-7,7-dimethyl-1-(3,4,5-trimethoxyphenyl)tetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazol-5-one (9b) and its (1*R**,2*R**)-epimer 9′b

Prepared from **3c** (205 mg, 0.70 mmol), **8** (75 µL, 0.90 mmol), and trifluoroacetic acid (45 µL, 0.6 mmol).

4.4.5 (1*R**,2*S**)-2-Acetyl-7,7-dimethyl-1-(3,4,5-trimethoxyphenyl)tetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazol-5-one (9b)

Yield: 43 mg (17%) of pale yellow solid. M. p. 142°C–149°C. – IR (ATR): $\nu = 2965$, 1710, 1694, 1593, 1456, 1437, 1360, 1231,

1123, 1009, 837, 654 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): $\delta = 1.13$ and 1.19 (6H, 2s, 2×7-CH_3), 2.04 (3H, s, $COCH_3$), 2.53 (1H, d, $J = 16.7$ Hz, 6-H_a), 2.59 (1H, d, $J = 16.8$ Hz, 6-H_b), 3.50 (1H, ddd, $J = 10.0$, 8.7, 6.9 Hz, 2-H), 3.60 (1H, t, $J = 10.5$ Hz, 3-H_a), 3.85 (3H, s, OCH_3), 3.86 (6H, s, 2×OCH_3), 3.89 (1H, dd, $J = 11.3$, 7.0 Hz, 3-H_b), 4.06 (1H, d, $J = 8.8$ Hz, 1-H), 6.68 (2H, s, 2H of Arl). – ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 23.2$, 29.3, 30.7, 42.3, 46.6, 56.4, 59.5, 61.0, 63.1, 64.4, 104.3, 135.0, 137.8, 153.6, 170.6, 204.9. – HRMS ((+)-ESI): $m/z = 363.19$ (calcd. 363.1914 for $C_{19}H_{27}N_2O_5$, $[M+H]^+$).

4.4.6 (1*R**,2*R**)-2-Acetyl-7,7-dimethyl-1-(3,4,5-trimethoxyphenyl)tetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazol-5-one (9′b)

Yield: 115 mg (45%) of pale yellow solid. M. p. 136°C–143°C. – IR (ATR): $\nu = 2944$, 1718, 1678, 1591, 1505, 1451, 1423, 1233, 1120, 1002, 821, 717 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): $\delta = 1.09$ and 1.25 (6H, 2s, 2×7-CH_3), 1.54 (3H, s, $COCH_3$), 2.49 (1H, d, $J = 16.6$ Hz, 6-H_a), 2.67 (1H, d, $J = 16.6$ Hz, 6-H_b), 3.72 (1H, dt, $J = 8.7$, 4.5 Hz, 2-H), 3.76–3.79 (1H, m, 3-H_a), 3.82–3.87 (10H, m, 3-H_b and 3×OCH_3), 4.22 (1H, d, $J = 8.7$ Hz, 1-H), 6.60 (2H, s, 2H of Arl). – ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 22.9$, 29.5, 31.4, 41.1, 47.2, 56.4, 58.4, 59.7, 61.1, 65.2, 105.3, 132.0, 138.1, 153.5, 170.0, 206.0. – HRMS ((+)-ESI): $m/z = 363.1919$ (calcd. 307.1208 for $C_{19}H_{27}ClN_2O_2$, $[M+H]^+$). – $C_{19}H_{26}N_2O_5 \cdot ½H_2O$: calcd. C 61.44, H 7.33, N 7.54; found C 61.68, H 7.16, N 7.58.

4.5 Synthesis of alkyl 5-acyl-1*H*-pyrazole-3-carboxylates 11a–f

Alkyl diazoacetate **10a**, **b** (1 mmol) was added to a solution of ynone **4** (1 mmol) in anhydrous acetonitrile (5 mL) and the so formed solution was stirred at room temperature for 24 h. Volatile components were evaporated *in vacuo* and the residue was triturated with diethyl ether (5 mL) and cooled to –15°C. The precipitate was collected by filtration to give **11a–f**. The following compounds were prepared in this manner:

4.5.1 Ethyl 5-[(*tert*-butoxycarbonyl)-L-alanyl]-1*H*-pyrazole-3-carboxylate (11a)

Prepared from ynone **4b** (39 mg, 0.20 mmol) and ethyl diazoacetate **10a** (21 µL, 0.20 mmol). Yield: 51 mg (80%) of pale yellow solid. M. p. 90°C–97°C. $-[\alpha]_D^{22} = -4.6$ ($c = 0.25$, CH_2Cl_2). – IR (ATR): $\nu = 3392$, 3189, 2978, 1726, 1677, 1528, 1284, 1208, 1163, 1019, 856, 726 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): $\delta = 1.38$ (3H, t, $J = 7.1$ Hz, CH_2CH_3), 1.47–1.52 (12H, m, 2′-CH_3 and Boc), 4.41 (2H, q, $J = 7.1$ Hz, CH_2CH_3), 5.47 (1H, p, $J = 7.2$ Hz, 2′-H), 5.64 (1H, d, $J = 7.7$ Hz, NHBoc), 7.38 (1H, s, 4-H), 12.66 (1H, br s, 1-NH). – ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 14.4$, 19.9, 28.5, 52.5, 61.7, 80.4, 110.7, 137.6, 147.6, 155.7, 159.5, 193.7. – HRMS ((+)-ESI): $m/z = 212.1039$ (calcd. 212.1030 for $C_9H_{14}N_3O_3$, $[M+H-Boc]^+$).

4.5.2 Ethyl 5-[(*tert*-butoxycarbonyl)glycyl]-1*H*-pyrazole-3-carboxylate (11b)

Prepared from ynone **4c** (100 mg, 0.54 mmol) and ethyl diazoacetate **10a** (52 µL, 0.49 mmol). Yield: 12 mg (8%) of white solid. M. p. 119°C–121°C. – IR (ATR): $\nu = 3390$, 3162, 2981, 1725, 1698, 1679, 1533, 1310, 1287, 1201, 1170, 845, 767 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): $\delta = 1.39$ (3H, t, $J = 7.1$ Hz, CH_2CH_3), 1.53 (9H, s, Boc), 4.41 (2H, q, $J = 7.2$ Hz, CH_2CH_3), 4.87 (2H, d, $J = 4.9$ Hz, CH_2NH), 5.63 (1H, t, $J = 4.8$ Hz, CH_2NH), 7.36 (1H, s, 4-H), 13.03 (1H, br s, 1-NH). – ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 14.4$, 28.5, 47.9, 61.7, 80.6, 109.8, 136.7, 148.8, 156.5, 159.2, 190.1. – HRMS ((+)-ESI): $m/z = 198.0865$ (calcd. 198.0873 for $C_8H_{12}N_3O_3$, $[M+H-Boc]^+$). – $C_{13}H_{19}N_3O_5$: calcd. C 52.52, H 6.44, N 14.13; found C 52.64, H 6.63, N 14.05.

4.5.3 Benzyl 5-[(*tert*-butoxycarbonyl)-L-alanyl]-1*H*-pyrazole-3-carboxylate (11c)

Prepared from ynone **4b** (61 mg, 0.31 mmol) and benzyl diazoacetate **10b** (51 µL, 0.31 mmol). Yield: 60 mg (51%) of pale yellow solid. M. p. 129°C–135°C. $-[\alpha]_D^{22} = -8.2$ ($c = 0.19$, CH_2Cl_2). – IR (ATR): $\nu = 3385$, 3169, 2979, 1726, 1675, 1531, 1285, 1166, 1005, 857 735, 693 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): $\delta = 1.46$–1.52 (12H, m, CH_3 and Boc), 5.34–5.40 (2H, m, CH_2), 5.49 (1H, dq, $J = 7.0$, 6.5 Hz, 2′-H), 5.67 (1H, d, $J = 7.7$ Hz, NHBoc), 7.32–7.43 (6H, m, 4-H and 5H of Ph), 12.84 (1H, br s, 1-NH). – ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 20.0$, 28.5, 52.5, 67.2, 80.5, 110.9, 128.5, 128.7, 128.8, 135.3, 137.2, 147.6, 155.7, 159.3, 193.7. – HRMS ((+)-ESI): $m/z = 274.1182$ (calcd. 274.1186 for $C_{14}H_{16}N_3O_3$, $[M+H-Boc]^+$).

4.5.4 Benzyl 5-[(*tert*-butoxycarbonyl)glycyl]-1*H*-pyrazole-3-carboxylate (11d)

Prepared from ynone **4c** (91 mg, 0.50 mmol) and benzyl diazoacetate **10b** (92 µL, 0.55 mmol). Yield: 64 mg (36%) of white solid. M. p. 153°C–155°C. – IR (ATR): $\nu = 3390$, 3160, 2981, 1727, 1699, 1675, 1532, 1289, 1197, 1171, 1130, 1007,

732 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): $\delta = 1.50$ (9H, s, Boc), 4.83 (2H, br s, C*H*$_2$NHBoc), 5.37 (2H, s, C*H*$_2$Ph), 5.58 (1H, br s, N*H*Boc), 7.32–7.42 (6H, 4-H and 5H of Ph), 12.95 (1H, br s, 1-NH). – ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 28.4$, 47.8, 67.1, 80.5, 109.8, 128.3, 128.6, 128.7, 135.1, 156.3, 158.9, 189.8. – HRMS ((+)-ESI): $m/z = 260.1018$ (calcd. 260.103 for $C_{13}H_{14}N_3O_3$, $[M + H - Boc]^+$).

4.5.5 Ethyl 5-acetyl-1*H*-pyrazole-3-carboxylate (11e) [32]

Prepared from ynone **4d** (39 µL, 0.50 mmol) and ethyl diazoacetate **10a** (55 µL, 0.52 mmol). Yield: 49 mg (54%) of pale yellow solid. ^1H NMR (500 MHz, $CDCl_3$): $\delta = 1.42$ (3H, t, $J = 7.1$ Hz, CH_2CH_3), 2.61 (3H, s, $COCH_3$), 4.43 (2H, q, $J = 7.1$ Hz, CH_2CH_3), 7.32 (1H, s, 4-H), 11.35 (1H, br s, NH). – HRMS ((+)-ESI): $m/z = 183.0765$ (calcd. 183.0764 for $C_8H_{11}N_2O_3$, $[M + H]^+$). Physical and spectral data are in agreement with the literature data [32].

4.5.6 Ethyl 5-benzoyl-1*H*-pyrazole-3-carboxylate (11f) [33]

Prepared from ynone **4e** (67 mg, 0.51 mmol) and ethyl diazoacetate **10a** (55 µL, 0.52 mmol). Yield: 71 mg (57%) of pale yellow solid. – ^1H NMR (500 MHz, $CDCl_3$): $\delta = 1.43$ (3H, t, $J = 7.1$ Hz, CH_2CH_3), 4.45 (2H, q, $J = 7.1$ Hz, CH_2CH_3), 7.42 (1H, s, 4-H), 7.52–7.56 (2H, m, 2H of Ph), 7.63–7.67 (1H, m, 1H of Ph), 8.08–8.11 (2H, m, 2H of Ph), 11.39 (1H, br s, NH). – HRMS ((+)-ESI): $m/z = 245.0915$ (calcd. 245.0921 for $C_{13}H_{13}N_2O_3$, $[M + H]^+$). Physical and spectral data were in agreement with the literature data [33].

4.6 Synthesis of *tert*-butyl (*S*)-(1-(3-arylisoxazol-5-yl)-1-oxopropan-2-yl)carbamates 13a, b

Ynone **4b** (203 mg, 1 mmol) was added to a solution of hydroxamoyl chloride **12a**, **b** (1 mmol) in anhydrous dichloromethane (5 mL) and the solution formed was stirred at room temperature for 2 min. Then, a solution of triethylamine (170–210 µL, 1.2–1.5 equiv.) in anhydrous dichloromethane (5 mL) was added slowly (~15 min) in several portions and the reaction mixture was stirred at room temperature for 24–72 h. The reaction mixture was washed with 1 M aq. $NaHSO_4$ (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and the filtrate was evaporated *in vacuo*. The residue was purified by FC (EtOAc-hexanes). Fractions containing the product were combined and evaporated *in vacuo* to give **13a**, **b**. The following compounds were prepared in this manner:

4.6.1 *tert*-Butyl (*S*)-(1-(3-phenylisoxazol-5-yl)-1-oxopropan-2-yl)carbamate (13a)

Prepared from **12a** (1.5 mmol) and **4b** (304 mg, 1.5 mmol). Yield: 180 mg (37%) of white solid. M. p. 123°C–128°C. – $[\alpha]_D^{22} = -1.2$ ($c = 0.31$, CH_2Cl_2). – IR (ATR): $\nu = 3328$, 2976, 1707, 1685, 1528, 1437, 1389, 1365, 1291, 1251, 1166, 1116, 1087, 1058, 1018, 945, 909, 860, 769, 695, 682, 628 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): $\delta = 1.45$ (9H, s, Boc), 1.51 (3H, d, $J = 7.2$ Hz, CH_3), 5.13 (1H, p, $J = 7.4$ Hz, 2′-H), 5.29–5.31 (1H, m, NH), 7.34 (1H, s, 4-H), 7.48–7.51 (3H, m, 3H of Ph), 7.83–7.85 (2H, m, 2H of Ph). – ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 18.2$, 28.4, 53.2, 80.4, 107.1, 127.0, 127.9, 129.3, 130.8, 155.2, 163.2, 165.3, 188.8. – HRMS ((+)-ESI): $m/z = 217.0977$ (calcd. 217.0972 for $C_{12}H_{13}N_2O_2$, $[M + H - Boc]^+$). – $C_{17}H_{20}N_2O_4$: calcd. C 64.54, H 6.37, N 8.86; found C 64.78, H 6.37, N 8.73.

4.6.2 *tert*-Butyl (*S*)-{1-[3-(2,6-dichlorophenyl)isoxazol-5-yl]-1-oxopropan-2-yl}carbamate (13b)

Prepared from **12b** (2 mmol) and **4b** (481 mg, 2.4 mmol). Yield: 236 mg (30%) of pale yellow solid. M. p. 118°C–121°C. – $[\alpha]_D^{22} = +2.1$ ($c = 0.18$, CH_2Cl_2). – IR (ATR): $\nu = 3391$, 2977, 1700, 1560, 1513, 1435, 1385, 1245, 1165, 1016, 783 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): $\delta = 1.46$ (9H, s, Boc), 1.55 (3H, d, $J = 7.2$ Hz, CH_3), 5.14 (1H, p, $J = 7.4$ Hz, 2′-H), 5.30–5.32 (1H, m, NH), 7.14 (1H, s, 4-H), 7.38 (1H, dd, $J = 9.0$, 7.1 Hz, 1H of $C_6H_3Cl_2$), 7.45 (2H, d, $J = 8.5$ Hz, 2H of $C_6H_3Cl_2$). – ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 18.1$, 28.3, 53.2, 80.3, 110.7, 127.0, 128.5, 131.6, 135.5, 155.0, 159.4, 164.8, 188.3. – HRMS ((+)-ESI): $m/z = 385.0717$ (calcd. 385.0716 for $C_{17}H_{19}Cl_2N_2O_4$, $[M + H]^+$).

4.6.3 *tert*-Butyl 2-{4-[(*tert*-butoxycarbonyl)-L-alanyl]-1*H*-1,2,3-triazol-1-yl}acetate (15)

Dichloromethane (3 mL), *tert*-butyl bromoacetate (0.1 mL, 0.68 mmol), and tetrabutylammonium bromide (66 mg, 0.21 mmol) were added to a solution of sodium azide (47 mg, 0.72 mmol) in water (4 mL). The mixture was stirred at room temperature for 40 h, the phases were separated, and ynone **4b** (138 mg, 0.70 mmol), CuI (44 mg, 0.23 mmol), and triethylamine (30 µL, 0.22 mmol) were added to the organic phase, and the reaction mixture was stirred at room temperature for 72 h. The reaction mixture was flash-chromatographed over silica gel

(EtOAc-hexanes, 2:1), fractions containing the product were combined and evaporated *in vacuo* to give **15**. Yield: 95 mg (38%) of yellow solid. M. p. 112°C–114°C. – $[\alpha]_D^{22} = +3$ ($c = 0.29$, CH_2Cl_2). – IR (ATR): $\nu = 3431$, 3396, 3095, 2981, 1740, 1717, 1703, 1690, 1514, 1246, 1156, 1038, 860, 749 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): $\delta = 1.44$ (9H, s, Boc), 1.50 (9H, s, Boc), 1.52 (3H, d, $J = 6.9$ Hz, CH_3), 5.08–5.17 (2H, m, CH_2), 5.33 (1H, p, $J = 6.8$ Hz, 2′-H), 5.44 (1H, d, $J = 6.3$ Hz, N*H*Boc), 8.29 (1H, s, 5-H). – ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 19.2$, 28.1, 28.5, 51.7, 53.2, 79.8, 84.6, 128.3, 145.8, 155.2, 164.6, 193.6. – HRMS ((+)-ESI): $m/z = 355.1969$ (calcd. 355.1976 for $C_{16}H_{27}N_4O_5$, $[M+H]^+$). – $C_{16}H_{26}N_4O_5$: calcd. C 54.22, H 7.39, N 15.81; found C 54.18, H 7.27, N 15.66.

4.6.4 Single-crystal X-ray structure analysis of compounds 7c, 9a, and 13a

Single-crystal diffraction data for all three compounds have been collected on an Agilent SuperNova dual-source diffractometer with an Atlas detector at room temperature with CuKα radiation ($\lambda = 1.54184$ Å using a mirror monochromator). The diffraction data were processed using CrysAlis Pro software [34]. All structures were solved by direct methods, using Sir97 [35]. Full-matrix least-squares refinements on F^2 were done with anisotropic displacement parameters for all nonhydrogen atoms. H atoms were placed at calculated positions and treated as the riding model. Shelxl-97 software [36] was used for structure refinement and interpretation. Drawings of the structures (cf. Figs. 3–5) were produced using Ortep-III [37–39]. Crystallographic data for all three compounds are summarized in Table 1.

Compound **7c** crystallizes in the very rare space group *P*1. There are two symmetry-independent molecules of **7c** with very similar conformation and one solvent chloroform molecule in the unit cell. At first glance, the independent molecules actually seem to be related by a center of inversion although, upon close inspection, the methyl groups at C5a and C5b seem to break this pseudo-symmetry as does the co-crystallized molecule chloroform. As a matter of fact, both molecules of **7c** have the same

Table 1: Crystallographic data for compounds **7c**, **9a**, and **13a**.

	7c	**9a**	**13a**
Empirical formula	$C_{45}H_{59}Cl_3N_6O_{16}$	$C_{16}H_{19}Cl_8N_2O_2$	$C_{17}H_{20}N_2O_4$
Moiety formula	$2\cdot(C_{22}H_{19}N_3O_8)\times(CHCl_3)$	$C_{16}H_{19}Cl_8N_2O_2$	$C_{17}H_{20}N_2O_4$
M_r	1046.34	306.78	316.35
Crystal size, mm^3	$0.28\times0.23\times0.10$	$0.35\times0.20\times0.10$	$0.30\times0.30\times0.10$
Crystal shape	Prism	Prism	Prism
Crystal system	Triclinic	Triclinic	Orthorhombic
Space group	*P*1 (no. 1)	$P\bar{1}$ (no. 2)	*Pbca* (no. 61)
a, Å	8.9424(3)	5.8846(4)	10.5449(3)
b, Å	9.8684(3)	10.8298(5)	9.8168(3)
c, Å	15.5641(6)	12.5646(9)	33.9041(9)
α, deg	77.411(3)	102.904(5)	90.0
β, deg	73.816(3)	90.328(5)	90.0
γ, deg	83.904(3)	91.695(5)	90.0
V, $Å^3$	1285.83(8)	780.10(8)	3509.66(17)
Z	1	2	8
$D_{calcd.}$, g cm^{-3}	1.351	1.306	1.197
μ(Cu*K*α), mm^{-1}	2.232	2.216	0.707
F(000), *e*	550	324	1344
hkl range	$-11\le h\le+11$	$-7\le h\le+6$	$-12\le h\le+12$
	$-11\le k\le+22$	$-11\le k\le+13$	$-11\le k\le+11$
	$-19\le l\le+18$	$-15\le l\le+15$	$-40\le l\le+40$
θ range, deg	3.0–73.7	3.6–74.7	3.9–69.6
Refl. total/unique	19 975/9368	7773/3181	7530/3242
R_{int}	0.026	0.033	0.021
Param. refined	647	193	217
$R(F)^a/wR(F^2)^b$	0.064/0.189	0.053/0.159	0.044/0.132
x(Flack)	0.04(2)	–	–
Δρ(max/min), *e* $Å^{-3}$	1.18/−0.62	0.26/−0.40	0.15/−0.16

[a]Reflections with $I > 2\sigma(I)$; [b]all reflections.

absolute configuration *S* at the chiral atoms C5a and C5b, respectively, which was also confirmed by the refinement of the Flack parameter ($x = 0.04(2)$). The space group $P1$ is enantiomorphic, which is in accordance with the observed optical activity of compound **7c**. The fact that there is only one molecule of chloroform in the unit cell is an additional confirmation of the noncentrosymmetric space group $P1$ because the chloroform molecule is not centrosymmetric. The centrosymmetric space group $P\bar{1}$ (no. 2) would require either one centrosymmetric solvent molecule or (at least) two noncentrosymmetric ones.

Nevertheless, to confirm additionally that the space group is not centrosymmetric $P\bar{1}$ (no. 2), a trial structure determination in this space group with the same unit cell parameters was performed. The result was a disordered structure. The structure was not ordered at the chiral center and in the region of solvent chloroform molecules. It was not possible to obtain any ordered racemate structure. Additionally, it was also checked if some other (more frequent than $P1$) enantiomorphic space group would agree with the diffraction data. Neither careful repeating of indexation of reflections nor checking for higher metrical symmetry gave any reasonable alternative solution. All these confirm that the correct space group of structure of **7c** is $P1$.

CCDC 1813945, 1813944, and 1813943 for compounds **7c**, **9a**, and **13a**, respectively, contain the supplementary crystallographic data for this article. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Graphical synopsis

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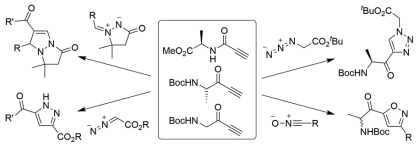
Synthesis of functionalized pyrazole derivatives by regioselective [3+2] cycloadditions of *N*-Boc-α-amino acid-derived ynones



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