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Construction of Spiro[3-azabicyclo[3.1.0]hexanes] via 1,3-Dipolar Cycloaddition of 1,2-Diphenylcyclopropenes to Ninhydrin-Derived Azomethine Ylides

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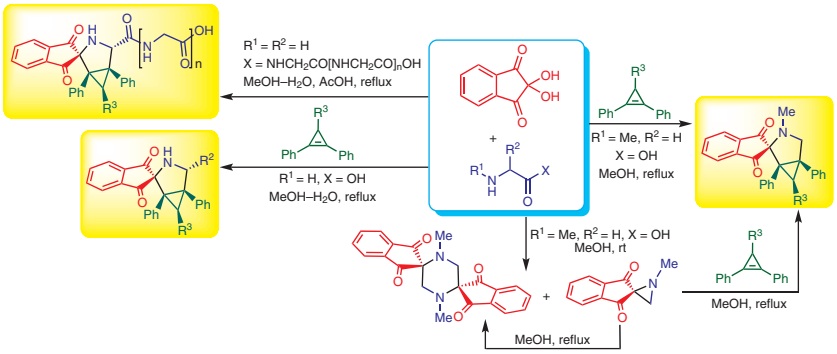
Dedicated to the memory of Dr. Yuri B. Koptelov



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Abstract The multi-component 1,3-dipolar cycloaddition of ninhydrin, α-amino acids (or peptides), and cyclopropenes for the synthesis of spirocyclic heterocycles containing both 3-azabicyclo[3.1.0]hexane and 2*H*-indene-1,3-dione motifs has been developed. This method provides easy access to 3-azabicyclo[3.1.0]hexane-2,2′-indenes with complete stereoselectivity and a high degree of atom economy under mild reaction conditions. A broad range of cyclopropenes and α-amino acids have been found to be compatible with the present protocol, which offers an opportunity to create a new library of biologically significant scaffold (3-azabicyclo[3.1.0]hexane). In addition, the comprehensive study of mechanism of azomethine ylide formation from ninhydrin and sarcosine was performed by means of M11 density functional theory (DFT) calculations. It has been revealed that experimentally observed 1-methylspiro[aziridine-2,2′-indene]-1′,3′-dione is a kinetically controlled product of this reaction and appears to act as a 1,3-dipole precursor. This theoretical study also shed light on the main transformations of the azomethine ylide derived from ninhydrin and sarcosine such as a 1,3-dipolar cycloaddition to cyclopropene dipolarophiles, a dimerization reaction and a (1+5) electrocyclization reaction. The antitumor activity of some synthesized compounds against cervical carcinoma (HeLa) cell line was evaluated in vitro by MTS-assay.

Key words cyclopropenes, α-amino acids, peptides, stereoselectivity, reaction mechanism, DFT calculations, antitumor activity, cervical carcinoma (HeLa) cell line

The 3-azabicyclo[3.1.0]hexane is an important bicyclic framework, which is a part of many natural products and pharmaceuticals with a wide range of biological activity.[1–3] The most remarkable among these compounds are serotonin-norepinephrine-dopamine reuptake inhibitors (SNDRI),[4] dopamine D_3 receptor antagonists,[5–7] inhibitors of dual leucine zipper kinase (DLK, MAP3K12),[8,9] histone deacetylase inhibitors,[2a] monoacylglycerol lipase (MAGL) inhibitors,[10] hepatitis C virus NS3/4A (HCV NS3/4A) protease inhibitors,[11] allosteric inhibitors of mutant isocitrate dehydrogenase type 1 (R132H IDH1),[12] 5-HT4 receptor partial agonists,[13] oxytocin receptor (OTR) antagonist,[14] inhibitors of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1),[15] and ghrelin receptor antagonists[16] (**I–VI**, Figure 1). In this context, considerable efforts have been made to develop general and straightforward methods for the preparation of the 3-azabicyclo[3.1.0]hexane derivatives. Nowadays, there is a number of effective synthetic procedures that provide access to the class of compounds: (a) decomposition of pyrazolines,[17] (b) Pd-catalyzed cyclopropanation of maleimides with *N*-tosylhydrazones,[18] (c) metal-catalyzed oxidative cyclization of 1,6-enynes,[19] (d) Pd-catalyzed stereoselective cyclopropanation of allenenes,[20] (e) Pd-catalyzed C–H cyclization of trifluoroacetimidoyl chlorides,[21] (f) Ag_2O-catalyzed oxidative cyclization of an amidinoester,[22]

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and (g) Au-catalyzed oxidative cyclopropanation of *N*-allylynamide.[23] In the past few years, the [3+2] cycloaddition process involving cyclopropenes and azomethine ylides has also been a popular method for the synthesis of 3-azabicyclo[3.1.0]hexanes.[24] It is essential to note that azomethine ylides generated in situ from glycine aldiminoesters can react with cyclopropenes in a highly enantioselecive manner in the presence of $Cu(MeCN)_4BF_4$ and chiral ligands.[24a,b] However, there is still a continued interest in creating simple and green methods that give rise to this rigid cyclopropane system.

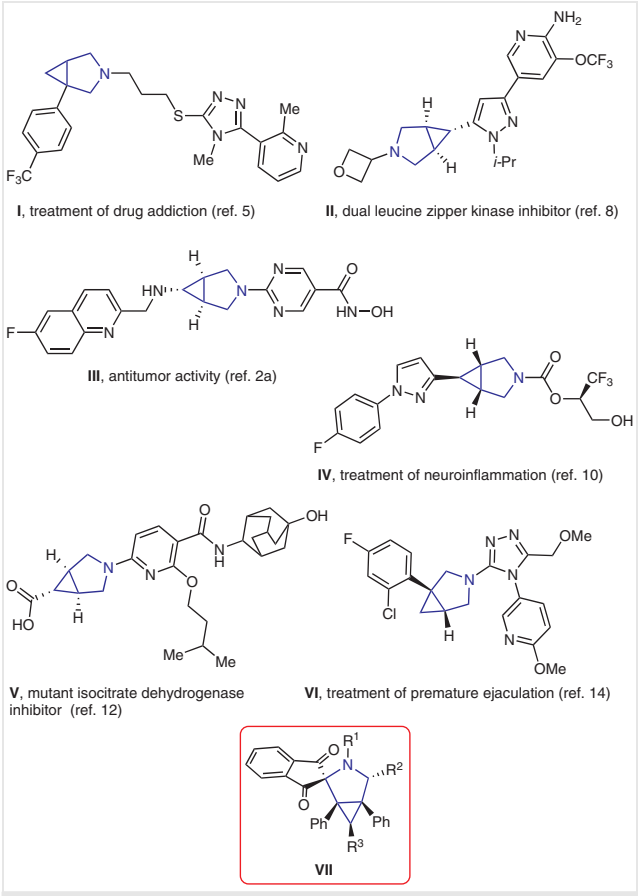
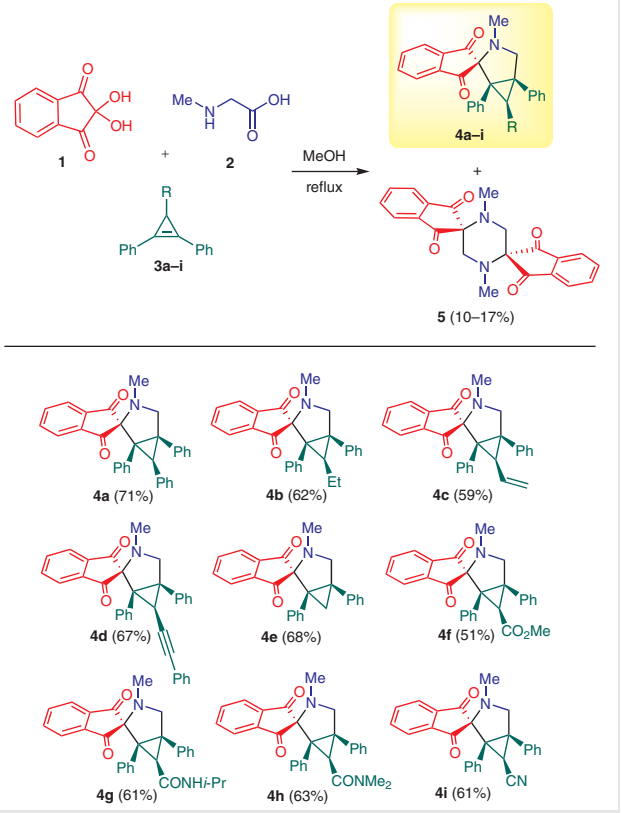


Figure 1 Selected bioactive 3-azabicyclo[3.1.0]hexane derivatives **I**–**VI** and spirocyclic scaffold **VII** from this study

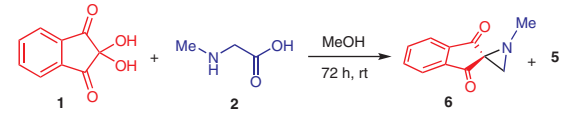
In recent years, multi-component 1,3-dipolar cycloadditions involving azomethine ylides derived from α-amino acids and 1,2-dicarbonyl compounds have received a great deal of attention since this method is a powerful and reliable tool that enables to form several bonds in one step as well as to avoid the isolation and purification of intermediate compounds.[25] Besides, the main benefit of azomethine ylide 1,3-dipolar cycloadditions is its concerted nature, resulting in diastereoselective formation of a wide range of heterocyclic frameworks. The realization of this three-component strategy for the synthesis of spirocyclic systems containing cyclopropane fragment was recently reported by our research group.[24c–e,26] In view of the relevance of use of 3-azabicyclo[3.1.0]hexane derivatives in medicinal chemistry, herein we report the study concerning the construction of new biologically significant 3-azabicyclo[3.1.0]hexane scaffold (**VII**, Figure 1) via a three-component approach using ninhydrin, α-amino acids (or simplest peptides), and cyclopropenes as substrates. It should be added that we have been able to isolate and characterize a new intermediate in the reaction of azomethine ylide formation from ninhydrin and sarcosine. Accordingly, based on Density Functional Theory (DFT) calculation data, considerable refinements have been made to the mechanism of the known reaction.

To probe the feasibility of the strategy, ninhydrin (**1**), sarcosine (**2**), and 1,2,3-triphenylcycloprop-1-ene (**3a**) were utilized as starting materials. Preliminary experiments have shown that methanol is the best solvent for the three-component 1,3-dipolar cycloaddition reaction. Upon treatment of **3a** with **1** and **2a** in methanol at reflux for 5 hours, cycloadduct **4a** was obtained in 71% yield (Scheme 1). The dimerization product **5** of the initially formed azomethine ylide was also isolated from the reaction mixture (10% yield). Regrettably, it was impossible to find reaction conditions under which the formation of by-product **5** would be completely suppressed. Next, we turned our attention to the scope and limitations of this reaction. A broad variety of cyclopropene substrates **3** were examined under the optimal conditions. The results are summarized in Scheme 1. The reactions smoothly proceeded with 1,2-diphenylcyclopropenes bearing different types of R substituents such as aryl, alkyl, alkenyl, alkynyl, alkoxycarbonyl, alkylamido, and nitrile groups. According to the experimental data, it can be seen that the electronic properties of the R substituents in cyclopropenes do not significantly affect reactivity. Cyclopropenes **3a**–**e** with electron-neutral or electron-donating R substituents gave the cycloadducts **4a**–**e** in moderate to good yields while cycloadducts **4f**–**i** containing electron-withdrawing groups were isolated in similar yields (Scheme 1). In all cases, the dimer **5** can be detected and isolated as a by-product in 10–17% yields (the reaction of ninhydrin with sarcosine has been reported to yield dispiropiperazine **5** after heating in methanol for 5 h).[27] All cycloadducts **4** and the azomethine ylide dimer **5** were fully characterized by IR, ^1H and ^{13}C NMR, and HRMS. Unfortunately, this reaction is limited to cyclopropenes containing only phenyl substituents at the double bond, whereas tetrasubstituted cyclopropenes, trisubstituted cyclopropenes bearing alkyl groups at the double bond, and unsubstituted at the double bond cyclopropenes, have proved to be nonreactive. For example, when using 3-methyl-1,2,3-triphenylcycloprop-1-ene, 2-phenyl-3-methyl-, and 2,3-dimethylcycloprop-2-enecarboxylates, as well as 3-methyl-3-phenylcyclopropene and methyl 1-methylcycloprop-2-enecarboxylate, cycloaddition reactions did not proceed.



Scheme 1 One-pot three-component reactions of ninhydrin (**1**), sarcosine (**2**), and cyclopropenes **3a–i**. *Reagents and conditions*: Unless otherwise indicated, the reactions were carried out with **1** (0.4 mmol), **2** (0.6 mmol), and **3** (0.4 mmol) in MeOH at reflux for 5 h. All products are racemic and isolated yields are shown.

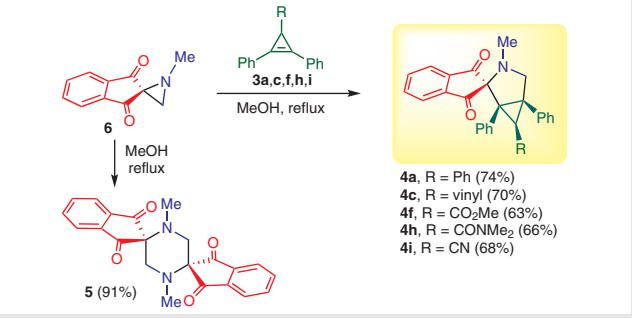
Previously, we described the cycloaddition reaction of the stable azomethine ylide from ninhydrin and L-proline with cyclopropenes.[26] In this study, we attempted to obtain a stable azomethine ylide from ninhydrin and sarcosine. For that purpose, equimolar quantities of ninhydrin (**1**) and sarcosine (**2**) were stirred in methanol at room temperature for 72 hours. The initially formed dark purple solution changed color to brown over time, and a light brown solid was precipitated. The solid was filtered and washed with cold methanol. The isolated product was investigated by NMR spectroscopy (^{1}H and ^{13}C). It was found that it is a mixture of two compounds in 4:1 ratio. In this case, the minor component is dispiropiperazine **5** (Scheme 2). There was no way to separate the components of the mixture chromatographically on SiO_2, since decomposition of the main component occurred. When neutral or basic alumina and Florisil were used as a stationary phase only adduct **5** was isolated, though it was contaminated with some unidentified decomposition by-products. Attempts to separate the mixture by crystallization were also unsuccessful. Consequently, the major component was characterized in the mixture with compound **5**. Its molecular formula, $C_{11}H_9NO_2$, was established by HRMS (ESI). An $[M + H]^+$ ion peak at m/z 188.0703 (calcd for $C_{11}H_{10}NO_2$: 188.0706) was observed. In the ^{13}C NMR spectrum ($CDCl_3$) of the mixture, compound **6** has signals at 71.9, 49.1 and 40.6 ppm, which are readily assigned to C_{spiro}, CH_2, and CH_3, respectively. For comparison, the signals of C_{spiro}, CH_2, and CH_3 for azomethine ylide dimer **5** are observed at 69.7, 54.2, and 40.2 ppm. The signals of aromatic protons are represented in the ^{1}H NMR spectra of compounds **5** and **6** by strongly coupled spin systems AA′BB′-type; however, for the former compound, they are located in a lower field range (7.86–8.02 ppm) compared to the signals of the second compound (7.68–7.80 ppm), which fully corresponds to their structural differences [Figure S23 in the Supporting Information (SI)]. In addition, the spectral differences of compounds **5** and **6** are manifested in the values of scalar constants $^1J_{C,H}$ for CH_2 groups. The registration of $^1J_{C,H}$ values was carried out using HSQC method without ^{13}C-decoupling, which allowed us to separate the satellite pairs of $C^{13}H_2$ proton signals according to the chemical shifts of carbon atoms for compounds **5** and **6**. In the usual ^{1}H NMR spectrum of a mixture of compounds **5** and **6**, the proton signals of all CH_2 groups are at 3.42 ppm and form a common broadened signal, the analysis of the structure and multiplicity of which is impossible. In contrast, the HSQCnd (nd–no ^{13}C-decoupling) spectrum shows that all CH_2 signals of the compound **5** have the same chemical shifts and the same values of constants $^1J_{C,H}$, which are equal to 142 Hz (Figure S24 in the SI). The chemical and magnetic equivalence of these protons indicates a high degree of symmetry of compound **5**. At the same time, it is clearly seen that for compound **6** the protons of the CH_2 group are chemically and magnetically nonequivalent, which manifests itself as AB-type doublet-doublet structures of the $C^{13}H_2$ satellite pair in the HSQCnd spectrum and two different values of heteronuclear scalar constants protons H′ and H″: $^1J_{C,H'}$ = 142 Hz, $^1J_{C,H''}$ = 137 Hz. Thus, based on the analysis of spectral data, the structure of 1-methylspiro[aziridine-2,2′-indene]-1′,3′-dione (**6**) was assigned to the major component. The aziridine structure is in good accordance with NMR spectral data since the chemical and magnetic inequivalence of the protons of the CH_2 group result from the high energy barrier for nitrogen inversion. Kuznetsov and co-workers previously described spirocyclic compounds with a similar skeleton.[28]



Scheme 2 The reaction of ninhydrin (**1**) and sarcosine (**2**) under mild conditions

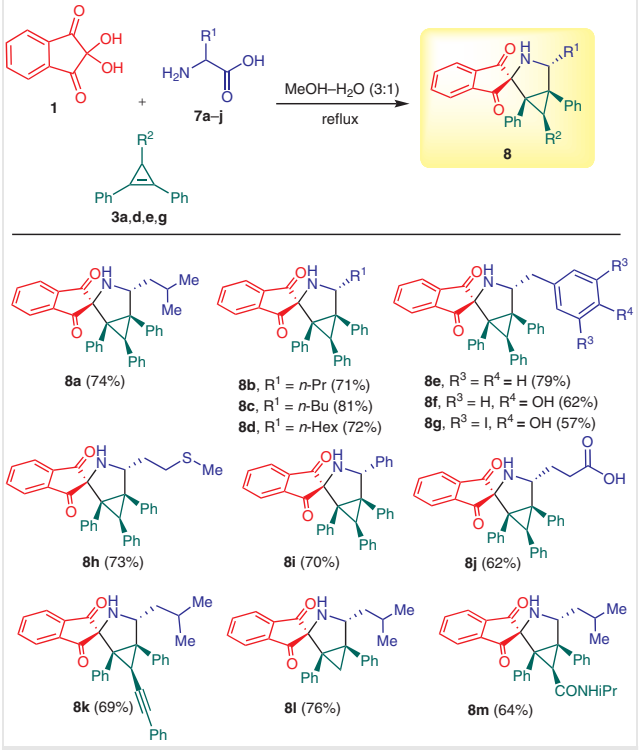
As noted above, aziridine **6** could not be isolated in pure form, therefore it was used in subsequent transformations as a mixture (4:1) with dispiropiperazine **5**. The presence of

compound **5** in the starting mixture does not influence the reactions involving aziridine **6**. In order to evaluate the ability of aziridine **6** to undergo ring-opening reaction resulting in the formation of 1,3-dipole, cyclopropene dipolarophile **3a** was selected as an azomethine ylide trap. Substrates **6** and **3a** did not react at room temperature in methanol, however, heating of the reaction mixture to the boiling point temperature of the reaction solvent led to the formation of **4a** in 74% yield. The progress of the reaction was monitored by ^{1}H NMR and TLC. Analysis of the reaction mixture showed the gradual disappearance of aziridine **6** signals and the appearance of cycloadduct **4a** signals. Next, we explored the scope of the reaction with a range of cyclopropenes **3c**,**f**,**h**,**i** as cycloaddition partners. A series of functional groups at the C3-position of cyclopropenes such as phenyl, vinyl, methoxycarbonyl, dimethylamido, and nitrile, were tolerated under the optimal reaction conditions, and the desired spiro[3-azabicyclo[3.1.0]hexanes] **4c**,**f**,**h**,**i** were obtained in good yields (Scheme 3). The ^{1}H NMR conversions for the starting aziridine **6** varied between 90 and 96%. We also found that when heating **6** in boiling methanol for 3 hours, it almost completely turned into dispiropiperazine **5** (Scheme 3). The reaction mechanism including the stage of aziridine **6** transformation was studied by a DFT computational method (vide infra).



Scheme 3 The ring opening reactions of aziridine **6** in the presence of cyclopropenes **3a**,**c**,**f**,**h**,**i**. All products are racemic and isolated yields are shown.

Next, we focused on exploring the substrate scope with respect to amino acids. We investigated three-component reactions involving some primary α-amino acids **7a–j**, cyclopropenes **3a**,**d**,**e**,**g**, and ninhydrin (**1**). The reactions smoothly proceeded in methanol–water on heating, giving spiro[3-azabicyclo[3.1.0]hexane-2,2′-indene]-1′,3′-diones **8** in acceptable yields with excellent diastereoselectivity (Scheme 4). Initially, the reaction of azomethine ylide in situ generated from ninhydrin (**1**) and alkyl-substituted α-amino acids **7a–d** with cyclopropene **3a** in methanol–water (3:1) at reflux led to the formation of racemic spirocyclic derivatives **8a–d** in 71–81% yields. In all cases, cyclopropenes were not completely consumed during the reactions. The structures of products **8a–d** were identified by means of ^{1}H and ^{13}C NMR, and HRMS. The structure of **8a** was further corroborated by single-crystal X-ray diffraction (Figure 2). In a similar way, the azomethine ylides [generated from ninhydrin (**1**) and L-phenylalanine (**7e**), L-tyrosine (**7f**), 3,5-diiodo-L-tyrosine (**7g**), L-methionine (**7h**), or DL-phenylglycine (**7i**)] reacted with **3a** to afford the racemic spiro[3-azabicyclo[3.1.0]hexanes] **8e–i** as single diastereomers in 57–79% yields. Additionally, L-glutamic acid (**7j**) has proved to be a suitable reactant, which in combination with ninhydrin (**1**) gave a 1,3-dipole. The latter was successfully trapped by 1,2,3-triphenylcycloprop-1-ene (**3a**) to furnish cycloadduct **8j** in 62% yield. Also, we examined the scope with respect to the cyclopropenes **3** in the reaction with azomethine ylide derived from ninhydrin (**1**) and L-leucine (**7a**) (Scheme 4). Three cyclopropene derivatives **3d**,**e**,**g** provided the corresponding products **8k–m** in good yields with excellent diastereoselectivities. Additionally, the ^{1}H NMR spectrum of the cycloadduct **8l** was recorded in the presence of a chiral shift reagent – praseodymium(III) tris[3-(heptafluoropropylhydroxymethylene)-D-camphorate] (Figure S50 in the SI). In accordance with the NMR spectrum, peak shape of the H-C4 methine proton at 3.9 ppm indicates that compound **8l** is a racemate. Unfortunately, all attempts to carry out three-component reactions involving glycine, L-alanine, L-serine, L-cysteine, L-histidine, or L-tryptophan failed.



Scheme 4 One-pot three-component synthesis of 3-azabicyclo[3.1.0]-hexane derivatives **8a–m**. *Reagents and conditions*: Unless otherwise indicated, reactions were carried out with **1** (0.4 mmol), **3** (0.4 mmol), and **7** (0.8 mmol) in MeOH–H_2O (3:1) at reflux for 10 h. All products are racemic and isolated yields are shown.

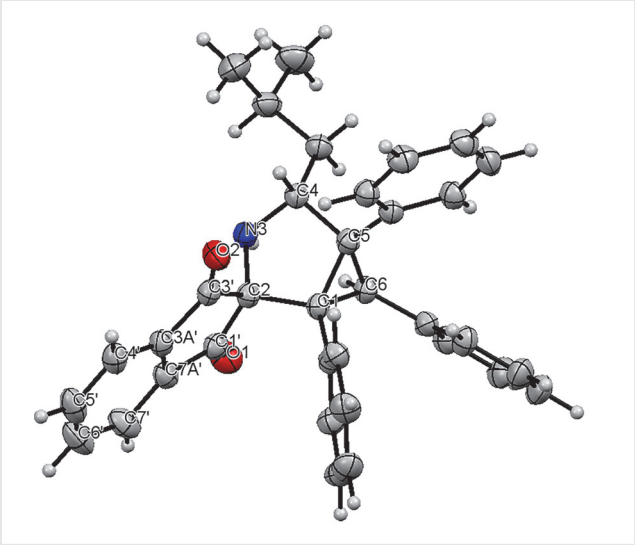


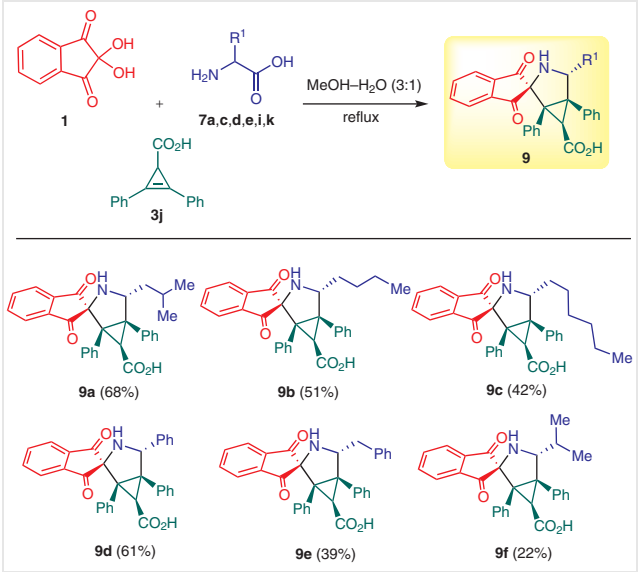
Figure 2 ORTEP representation of the molecular structure of **8a**

Since new derivatives of 3-azabicyclo[3.1.0]hexane-6-carboxylic acid may be of interest for biomedical research,[12] we tried to synthesize compounds containing this structural fragment by carrying out one-pot three-component 1,3-dipolar cycloaddition reactions of 2,3-diphenylcycloprop-2-enecarboxylic acid (**3j**) with azomethine ylides generated from ninhydrin (**1**) and several primary α-amino acids **7**. As depicted in Scheme 5, when amino acids **7a**,**c**,**d** were applied as reactants under standard conditions, racemic 4-alkyl-3-azabicyclo[3.1.0]hexane-6-carboxylic acids **9a–c** were obtained in 42–68% yields. In the same way, DL-phenylglycine (**7i**) worked well, thus leading to **9d** in 61% yield. The 1,3-dipolar cycloaddition of azomethine ylide generated from ninhydrin (**1**) and L-phenylalanine (**7e**) to cyclopropene **3j** afforded the corresponding compound **9e** in moderate yield (39%). When the reaction of azomethine ylide derived from ninhydrin (**1**) and L-valine (**7k**) with cyclopropene **3j** was carried out under standard conditions, product **9f** was obtained in modest yield (22%). This can be caused by a diminished reactivity of such azomethine ylide toward 1,3-dipolar cycloaddition due to the presence of a bulky isopropyl group located near the reaction center of the 1,3-dipole. The structures of the resultant cycloadducts were established by considering their ^{1}H and ^{13}C NMR spectra. To the best of our knowledge, these reactions are the first examples of a one-stage preparation of 3-azabicyclo-[3.1.0]hexane-6-carboxylic acids via the 1,3-dipolar cycloaddition reaction.

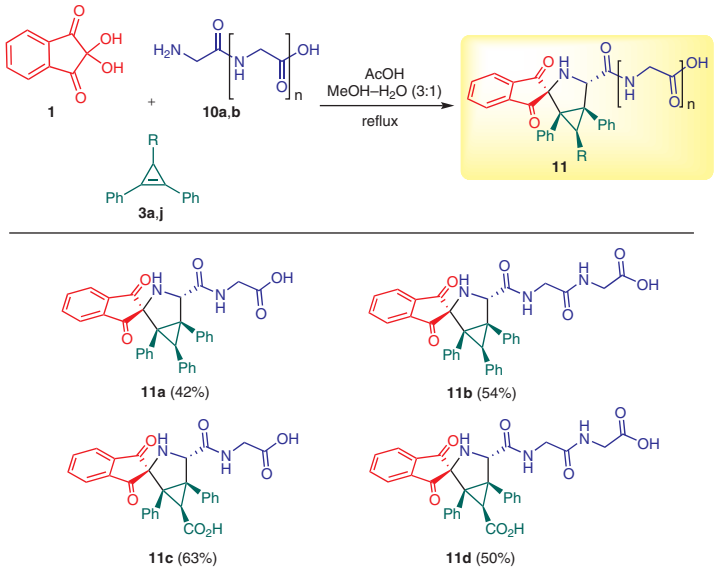
In previous studies, we reported the 1,3-dipolar cycloaddition of azomethine ylides derived from isatins, 11*H*-indeno[1,2-*b*]quinoxalin-11-one or tryptanthrins, and simplest peptides with cyclopropene dipolarophiles.[24c–e] In that work, under the optimized conditions for [3+2] cycloaddition reactions [AcOH (10 equiv), MeOH–H_2O (3:1), reflux], the synthesis of four 3-azabicyclo[3.1.0]hexane derivatives with a peptide fragment were conducted using Gly-Gly (**10a**) or Gly-Gly-Gly (**10b**) and cyclopropenes **3a**,**j** (Scheme 6). Reactions of the azomethine ylides generated from ninhydrin (**1**) and peptides **10a**,**b** with dipolarophiles **3a**,**j** gave products **11a–d** in 42–63% yields (in all reactions incomplete conversion of cyclopropene substrate was observed). All 1,3-dipolar cycloadditions involving nitrogen ylides derived from peptides **10** were found to be highly diasteoselective. The compounds **11** were isolated as a single diastereomer.

As discussed above, the reaction between sarcosine (**2**) and ninhydrin (**1**) in MeOH at room temperature results in the formation of a previously unknown spiroaziridine **6** (Scheme 7). Currently, spiroaziridine **6** is not mentioned in any studies on 1,3-dipolar cycloaddition reactions involving the azomethine ylide **12** generated from ninhydrin (**1**) and sarcosine (**2**). There are only a few hypotheses regarding the mechanism of azomethine ylide **12** formation from ninhydrin (**1**) and sarcosine (**2**). It is believed that the condensation reaction of **1** with **2** (MeOH, reflux) initially leads to the formation of spirolactone **14**, which subsequently loses carbon dioxide as a result of retro-1,3-dipolar cycloaddition to generate the 1,3-dipole **12**.[29]

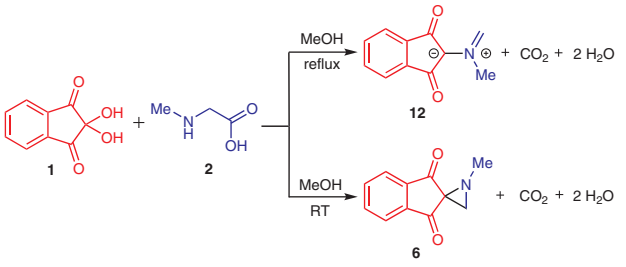
In turn, the resulting azomethine ylide **12** can be not isolated since it immediately undergoes either the 1,5-electrocyclization or dimerization reaction.[27,29,30] Several studies have been published concerning subsequent transformations of azomethine ylide **12**. More than 30 years ago, Grigg and co-workers have reported that the in situ generated 1,3-dipole **12** is prone to the 1,5-electrocyclization re-



Scheme 5 One-pot three-component synthesis of 3-azabicyclo[3.1.0]-hexane-6-carboxylic acids **9a–f**. *Reagents and conditions*: Unless otherwise noted, all reactions were carried out with **1** (0.4 mmol), **3j** (0.4 mmol), and **7** (0.8 mmol) in 15 mL MeOH–H_2O (3:1) at reflux for 10 h. All products are racemic and isolated yields are shown.



Scheme 6 One-pot three-component synthesis of 3-azabicyclo[3.1.0]hexanes **11a–d** with peptide fragments. *Reagents and conditions*: **1** (0.4 mmol), **3** (0.4 mmol), **10** (0.6 mmol), AcOH (50 µL) in 20 mL MeOH–H_2O (3:1) at reflux for 8 h. All products are racemic and isolated yields are shown.



Scheme 7 The condensation reaction between ninhydrin (**1**) and sarcosine (**2**) resulting in the formation of azomethine ylide **12** and aziridine **6**

action to give 3-methyl-2,3-dihydro-4*H*-indeno[2,1-*d*]oxazol-4-one (**15**) (vide infra) in the absence of dipolarophiles.[29] In 2008, during the study of 1,3-dipolar cycloaddition reactions involving this ninhydrin-derived azomethine ylide **12**, Bandyopadhyay's research group provided results, which were contrary to Grigg's findings.[27] In this study, the ylide **12** generated from **1** and **2** (MeOH, reflux, 5 h) was also found to be unstable. Its subsequent conversion is accompanied by the formation of dispiro[indene-2,2′-piperazine-5′,2″-indene] derivative **5** resulting from the dimerization reaction. The structure of dimerization product was identified on the basis NMR spectroscopy and mass spectral analysis. Additionally, the condensation reaction of ninhydrin (**1**) and sacrosine (**2**) was considered by Sudha's research team.[30] Dispiropiperazine **5** was obtained as a result of the solvent-free microwave-assisted $BiCl_3$-catalyzed condensation reaction between **1** and **2**. Eventually, the structure of dimer **5** was unequivocally corroborated by X-ray crystal structure analysis, and a comprehensive description of the crystal structure was presented in that study. To date, however, no theoretical studies concerning the condensation reaction of ninhydrin (**1**) and sarcosine (**2**) and subsequent transformations of the resulting 1,3-dipole **12** have been presented. Accordingly, there are no data, which make it possible for researchers to rationalize the experimental results in this field of organic chemistry.

In this paper, we have experimentally established that spiroaziridine **6** is a stable compound at room temperature and acts as a precursor of azomethine ylide **12**. As shown above, heating of the aziridine **6** in methanol in the presence of cyclopropenes **3** results in the formation of classic [3+2] cycloadducts – spiro-3-azabicyclo[3.1.0]hexanes **4**, while thermal aziridine transformation in the absence of dipolarophiles leads to azomethine ylide dimer **5**. This suggests that aziridine **6** undergoes a thermal ring-opening reaction to give the in situ generated nitrogen ylide **12** which, in turn, could be involved in intermolecular [3+2] and [3+3] cycloadditions. In this way, we thought it necessary to perform a theoretical study regarding the mechanism of the ninhydrin-derived azomethine ylide **12** formation as well as to shed light on azomethine ylide **12** transformations such as the 1,5-electrocyclization reaction, the [3+2] cycloaddition to cyclopropenes, and the [3+3] cycloaddition (the dimerization reaction). It is also important to determine whether spiroaziridine **6** is a kinetically controlled product of the condensation reaction between ninhydrin (**1**) and sarcosine (**2**).

Calculations at DFT/HF level of theory using M11 hybrid exchange-correlation functional and cc-pVDZ basis set were carried out to optimize the geometry of reactants,

products, and transition state structures (TSs). At the beginning of the theoretical study, the calculation of the Gibbs free energy change for the reaction of azomethine ylide **12** formation from sarcosine (**2**) and ninhydrin (**1**) was performed (Scheme 7, Table 1). Products of this reaction along with azomethine ylide **12** are two molecules of water and carbon dioxide. This transformation has proved to be an exergonic process occurring with a decrease in the Gibbs free energy (ΔG = –16.1 kcal/mol) (Table 1, entry 1).

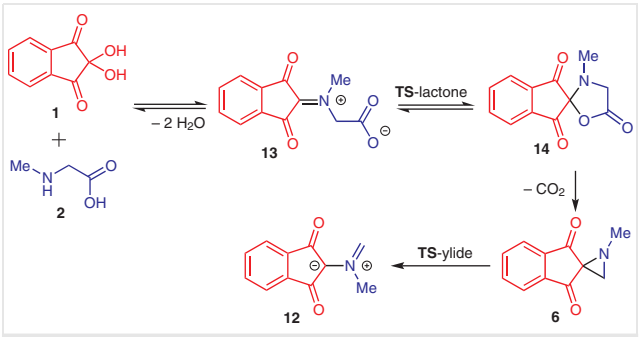
Table 1 The Reaction Mechanism of Azomethine Ylide **12** Formation from Ninhydrin (**1**) and Sarcosine (**2**)[a]

Entry	Reaction	Transition	$\Delta G^{‡}$, kcal/mol	ΔG, kcal/mol
1	**1** + **2** → **12**	**1** + **2** → **12**	–	–16.1
2	**1** + **2** → **6**	**1** + **2** → **6**	–	–11.3
3	**13** → **14**	**13** → **TS**-lactone	1.6	–
4	**13** → **14**	**13** → **14**	–	–16.2
5	**14** → **6**	**14** → **6**	–	–9.9
6	**6** → **12**	**6** → **TS**-ylide	29.6	–
7	**6** → **12**	**6** → **12**	–	–4.8

[a] Relative free energy change between reactants and transition states (free energies of activation $\Delta G^{‡}$) and relative free energy change between reactants and products (ΔG) are given in kcal/mol.

We also calculated the change in the Gibbs free energy for the reaction in which the final product is aziridine **6** rather than azomethine ylide **12**. This reaction is also a thermodynamically favorable process (ΔG = –11.3 kcal/mol) (Table 1, entry 2). However, azomethine ylide **12** is ca. 4.8 kcal/mol more thermodynamically stable than aziridine **6** (entries 1, 2). This means that the transformation of aziridine **6** into azomethine ylide **12** should be a spontaneous reaction. Next, we focused on studying the mechanism of azomethine ylide **12** formation.

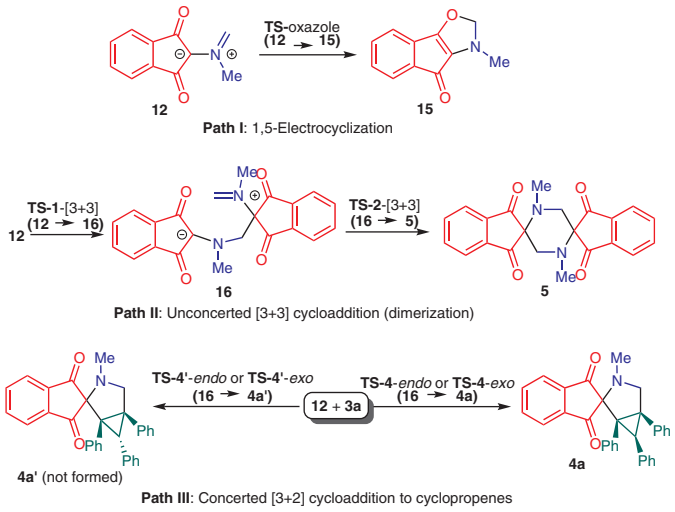
The first intermediate formed by the reaction of **1** with **2** is a zwitterion compound **13** (Scheme 8). The latter smoothly converts into spirolactone **14** as a result of the 1,5-electrocyclization reaction via **TS**-lactone. The Gibbs energy of activation ($\Delta G^{‡}$) for this transformation is ca. 1.6 kcal/mol (Table 1, entries 3, 4; Figure S74 in the SI). Then the direct transformation of spirolactone **14** into aziridine **6** appears to occur (Scheme 8). This reaction is thermodynamically favorable, since the Gibbs free energy change for this transformation is –10 kcal/mol (entry 5). Unfortunately, we have been unable to find the transition state corresponding to the direct conversion of spirolactone **14** into spiroaziridine **6**. It is expected that the aziridine cycle is formed through the transition state in which the cycloreversion of carbon dioxide and 1,3-electrocyclization take place simultaneously. This transition state is consistent with the general principles of organic chemistry and can probably be found in analyzing the potential energy surface (PES). The mechanism of aziridine **6** formation from zwitterion compound **13** could be suggested as an alternative. In this case, there should also be the transition state structure in which the C–C=O bond is broken and the C–C bond is formed, that is, 3-*endo-trig* cyclization occurs. However, such transformation is prohibited by Baldwin's rules. Thus, aziridine **6** is more likely to be formed from spirolactone **14**.



Scheme 8 The proposed mechanism for azomethine ylide **12** generation from sarcosine (**2**) and ninhydrin (**1**)

Then, we examined the experimentally observed transformation of **6** into **12** (Scheme 8, Table 1). Having found the transition state **TS-ylide** corresponding to the ring-opening reaction of an aziridine cycle, we calculated the Gibbs energy of activation ($\Delta G^{‡}$) for this transformation and obtained a value equal to 29.6 kcal/mol (Table 1, entry 6). Generally, the thermodynamically favorable reactions with the value of Gibbs energy of activation ca. 30 kcal/mol or higher are kinetically inhibited at room temperature. Aziridine **6** is a stable compound at room temperature and does not convert to azomethine ylide **12**. In this context, the value of Gibbs energy of activation for the transformation is completely compatible with the experimental data and explains why aziridine **6** does not transform into ylide **12** at room temperature. However, it is possible to overcome the energy barrier at elevated temperatures, and the conversion of aziridine **6** into a more stable azomethine ylide **12** is getting kinetically favorable (entries 6, 7; Figure S74 in the SI).

Next, we concentrated on studying the main transformations of azomethine ylide **12** (Scheme 9, Table 2). The 1,5-electrocyclization reaction leading to oxazole **15**, dimerization of azomethine ylide **12**, and [3+2] cycloaddition reaction to 1,2,3-triphenylcycloprop-1-ene (**3a**) were thoroughly examined. Based on the calculated data, there is evidence that the 1,5-electrocyclization of azomethine ylide **12** to oxazole derivative **15** is an endergonic reaction because the free energy change for this transformation is ca. 16.7 kcal/mol (ΔG >0) (Table 2, entries 1, 2; Figure S74 in the SI). Then, we studied the experimentally confirmed [3+3] cycloaddition reaction involving two azomethine ylide molecules. When analyzing the potential energy surface (PES), the dimerization reaction of azomethine ylide **12** is found to proceed by a two-step mechanism (Scheme 9,



Scheme 9 The main transformations of azomethine ylide **12** derived from sarcosine (**2**) and ninhydrin (**1**)

entries 3–7). The first step of [3+3]-cycloaddition reaction is rate-determining ($\Delta G^{\ddagger}$ = 15.1 kcal/mol) (entry 3). The Gibbs energy of activation ($\Delta G^{\ddagger}$) for first step is satisfactory in order to allow reaction to be kinetically favorable at 60 °C. The value of Gibbs free energy of activation for the second stage is 7 kcal/mol (entry 5). Betaine **16** is energetically less stable than starting two azomethine ylide molecules (entry 4). So that means that intermediate **16** cannot be isolated in pure form due to its spontaneous conversion into the corresponding dispiropiperazine **5** (entry 6; Figure S74 in the SI).

Finally, the [3+2] cycloaddition reaction of azomethine ylide **12** to cyclopropenes **3** was investigated. To study kinetics and thermodynamics of this process, we considered the reaction with one of the most active cyclopropenes – 1,2,3-triphenylcyclopropene (**3a**) (Table 2; Figure S75in the SI). Theoretically, in case of a concerted mechanism, the [3+2] cycloaddition reaction may proceed through four transition states. Full geometry optimization of the four possible transition states **TS-4a**-*endo*, **TS-4a**-*exo*, **TS-4a′**-*endo* and **TS-4a′**-*exo* for the reaction between 1,2,3-triphenylcycloprop-1-ene (**3a**) and azomethine ylide **12** was successfully carried out using M11/cc-pVDZ (Table 2, entries 8–13; Figure S75 in the SI). Two of these transition states **TS-4a**-*endo* and **TS-4a**-*exo* give rise to the diastereomer **4a** with three *cis*-located phenyl groups, while **TS-4a′**-*endo* and **TS-4a′**-*exo* correspond to the diastereomer **4a′**, which has the opposite configuration of the asymmetric C3 carbon atom. Each of the diastereomers **4a** and **4a′** is a mixture of two invertomers.

However, there is no point to consider them separately because pyramidal inversion for 3-azabicyclo[3.1.0]hexane derivatives is very rapid at room temperature. According to values of Gibbs energy of activation ($\Delta G^{\ddagger}$), the *endo* and *exo* approaches leading to diastereomer **4a** are more favorable than the *endo* and *exo* ones corresponding to opposite diastereomer **4a′** (Table 2, entries 8–11; Figure S75 in the SI). **TS-4a**-*endo* and **TS-4a**-*exo* are more energetically stable than their corresponding **TS-4a′**-*endo* and **TS-4a′**-*exo* (ca. 5.9 kcal/mol and 10.2 kcal/mol, respectively). This explains

Table 2 Theoretical Investigation of the Main Azomethine Ylide **16** Transformations: 1,5-Electrocyclization, Dimerization reaction, and [3+2] Cycloaddition[a]

Entry	Reaction	Transition	$\Delta G^{\ddagger}$, kcal/mol	ΔG, kcal/mol
1,5-Electrocyclization				
1	**12** → **15**	**12** → **TS**-oxazole	22.4	–
2	**12** → **15**	**12** → **15**	–	16.7
Dimerization reaction ([3+3] cycloaddition)				
3	**12** → **16**	**12** → **TS-1**-[3+3]	15.1	–
4	**12** → **16**	**12** → **16**	–	10.0
5	**16** → **5**	**16** → **TS-2**-[3+3]	7.0	–
6	**16** → **5**	**16** → **5**	–	–28.5
7	**12** → **5**	**12** → **5**	–	–18.5
[3+2] Cycloaddition reaction				
8	**12** + **3a** → **4a**	**12** → **TS-4a**-*endo*	14.0	–
9	**12** + **3a** → **4a**	**12** → **TS-4a**-*exo*	15.5	–
10	**12** + **3a** → **4a′**	**12** → **TS-4a′**-*endo*	19.9	–
11	**12** + **3a** → **4a′**	**12** → **TS-4a′**-*exo*	25.7	–
12	**12** + **3a** → **4a**	**12** → **4a**	–	–31.8[b]
13	**12** + **3a** → **4a′**	**12** → **4a′**	–	–30.3[b]

[a] Relative free energy change between reactants and transition states (free energies of activation $\Delta G^{\ddagger}$) and relative free energy change between reactants and products (ΔG) are given in kcal/mol.
[b] To calculate the change in Gibbs energy for the transformation **12** + **3a** → **4a** and **12** + **3a** → **4a′**, the energies of more stable invertomers are used.

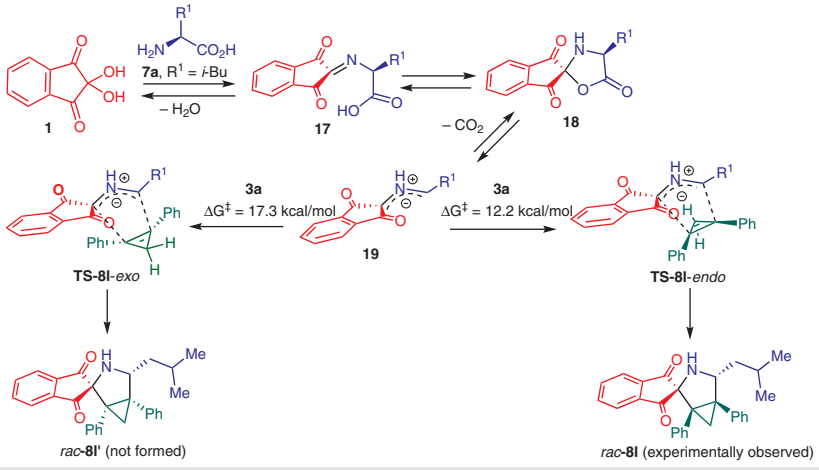
complete diastereofacial stereoselectivity of 1,3-dipolar cycloaddition reaction between azomethine ylide **12** and 1,2,3-triphenylcycloprop-1-ene (**3a**). Additionally, [3+2] cycloaddition of ylide **12** to **3a** ($\Delta G^{\ddagger}$ = 14.0 kcal/mol) is more kinetically preferable than dimerization reaction ($\Delta G^{\ddagger}$ = 15.5 kcal/mol) that is in good accordance with experimental results. Azomethine ylide **12** is actually more prone to react with cyclopropene dipolarophiles than to undergo a dimerization reaction.

Thus, we have revised the mechanism of azomethine ylide **12** formation. Moreover, the main transformations of azomethine ylide **12** have been discussed. The azomethine ylide **12** formation appears to proceed via intermediate formation of spirolactone **14** and spiroaziridine **6**. There are only two main transformations that are characteristic for azomethine ylide **12** – [3+2] cycloaddition reaction and the dimerization reaction. If the 1,2-diphenylcyclopropene derivative **3** acts as a dipolarophile, [3+2] cycloaddition is more kinetically favorable than dimerization reaction.

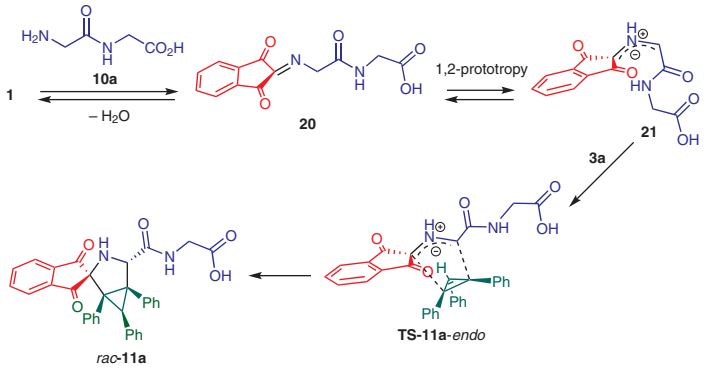
During our theoretical study, the mechanism of azomethine ylide formation from sarcosine (**2**) and ninhydrin (**1**) was studied in detail. It was disclosed that one of the intermediates that is formed during azomethine ylide **12** formation is spiro[aziridine-2,2′-indene]-1′,3′-dione (spiroaziridine) **6**, which was characterized by spectral methods for the first time. The resulting aziridine **6** is a stable precursor of azomethine ylide **12**. On heating **6** undergoes a ring-opening reaction to give 1,3-dipole **12**, which can be readily trapped with cyclopropene dipolarophiles **3** to form the corresponding [3+2] cycloadducts **4**. Conversely, aziridine **6** transformation in heating methanol in the absence of dipolarophiles results in the formation of dispiropiperazine **5**, which is a dimerization product of azomethine ylide **12**. Spiroaziridine **6** is less thermodynamically stable than 1,3-dipole **12**, and the conversion of **6** to azomethine ylide **12** is characterized by a high free energy of activation ($\Delta G^{\ddagger}$ = 29.6 kcal/mol). This fact accounts for aziridine stability at low temperatures. In turn, the values of free energy of activation for reactions involving azomethine ylide **12** – [3+2] cycloaddition (~14 kcal/mol) and [3+3] cycloaddition (~15.1 kcal/mol) indicate that 1,3-dipolar cycloaddition to cyclopropenes **3** has priority over the dimerization reaction.

We also theoretically investigated the reaction involving azomethine ylide **19** [generated from L-leucine (**7a**) and ninhydrin (**1**)] and 1,2-diphenylcyclopropene (**3e**) to elucidate stereoselectivity of this 1,3-dipolar cycloaddition reaction (Scheme 10). The azomethine ylide **19** generation is believed to proceed through intermediate formation of imine **17** and spirolactone **18**. To evaluate the Gibbs energy of activation ($\Delta G^{\ddagger}$) of *endo* and *exo* approaches, the full geometry optimization of the two possible transition states **TS-8l**-*endo* and **TS-8l**-*exo* was carried out. Having obtained both optimized geometries, it has been revealed that *endo* cycloaddition is kinetically more favorable than *exo* one. This calculation data is in full agreement with experimental results. Simultaneously, the *endo* cycloadduct **8l** is also a thermodynamically controlled product of this reaction (Table S2 in the SI). Apparently, **TS-8l**-*endo* prevailed over **TS-8l**-*exo* due to favorable N_{ylide}–$H_{cyclopropene}$ secondary orbital interactions [the distance in **TS-8l**-*endo* between ylide nitrogen atom and *endo* cyclopropene hydrogen atom is ca. 2.40 Å that is considerably shorter than the N–H van der Waals radius (rw = 2.65 Å)].[26]

In the same way, azomethine ylides derived from ninhydrin (**1**) and peptides **10a**,**b** cycloadd to cyclopropenes **3a**,**j** with complete *endo* selectivity with the approach of 1,3-dipole from a less-hindered face of cyclopropenes to give cycloadducts **11**. It is worth mentioning that azomethine ylide **21** appears to be formed from intermediate imine **20** as a result of thermal 1,2-prototropy (Scheme 11).



Scheme 10 The proposed reaction mechanism for the reaction of ninhydrin (**1**), L-leucine (**7a**), and 1,2-diphenylcyclopropene (**3e**)



Scheme 11 The proposed reaction mechanism for the reaction of ninhydrin (**1**), Gly-Gly (**10a**), and 1,2,3-triphenylcycloprop-1-ene (**3a**)

The cytotoxic activity of some of the newly synthesized compounds against human cervical carcinoma (HeLa) cell line was evaluated in vitro by the standard MTS assay for 24 and 72 hours. The results of these investigations are presented in Figures 3 and 4. It was found that among these compounds with spiro-fused 3-azabicyclo[3.1.0]hexane and 2*H*-indene-1,3-dione moieties only **8f**, which has 4-hydroxybenzyl substituent at pyrrolidine ring, demonstrates significant activity: IC_{50} 24.5 ± 2.4 μg/mL (44.7 ± 4.6 μM) for 24 hours (Figure 3) and 9.6 ± 1.4 μg/mL (17.5 ± 2.7 μM) for 72 hours (Figure 4). The observed decrease in cell viability under the action of substances **8a** and **8h** is explained by a decrease in the cell number after the treatment for 72 hours compared to the control (cells slowed down their division compared to the control, but remain alive). It was found that compound **8f** demonstrates less cytotoxic activity against benign cell line (Vero): IC_{50} 56.9 ± 1.7 μg/mL for 24 hours and 23.6 ± 1.6 μg/mL for 72 hours. These results indicated that spiro[3-azabicyclo[3.1.0]hexanes] with 2*H*-indene-1,3-dione motif may be useful leads for further biological screenings. Evaluation of their biological activities against other cell lines is in progress currently.

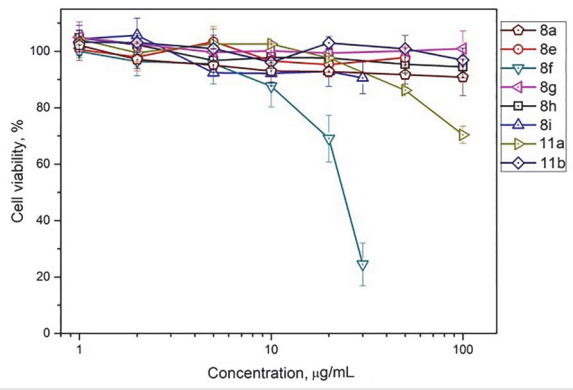


Figure 3 Cytotoxicity of compounds **8a**, **8e–i** and **11a**,**b** against the cervical carcinoma (HeLa) cell line (24 h)

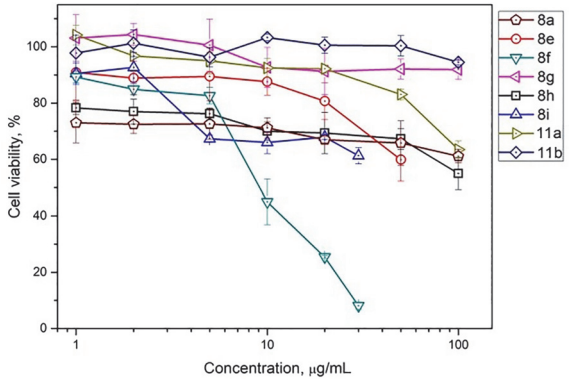


Figure 4 Cytotoxicity of compounds **8a**, **8e–i** and **11a**,**b** against the cervical carcinoma (HeLa) cell line (72 h)

In summary, we have developed an efficient method for the synthesis of spirocyclic systems containing both 3-azabicyclo[3.1.0]hexane and 2*H*-indene-1,3-dione moieties via multi-component reaction of ninhydrin, α-amino acids (or peptides), and cyclopropenes. The present method provides an effective approach to spirocyclic 3-azabicyclo[3.1.0]hexane-2,2′-indenes with exclusive stereoselectivity in an efficient and atom-economical manner under mild reaction conditions. In this study, we postulate the formation of 1-methylspiro[aziridine-2,2′-indene]-1′,3′-dione – a kinetically controlled product of reaction between ninhydrin and sarcosine, which seems to act as a source of reactive azomethine ylide. The reaction mechanisms of condensation reaction between sarcosine and ninhydrin, including the stage of aziridine transformation, and 1,3-dipolar cycloaddition reactions of cyclopropenes to azomethine ylides from ninhydrin were studied by means of DFT calculations. Additionally, the antitumor activity of some synthesized compounds against cervical carcinoma (HeLa) cell line was evaluated by MTS-assay in vitro.

NMR spectra were recorded with Bruker Avance 400 spectrometer (400.13 MHz for ^{1}H and 100.61 MHz for ^{13}C). Chemical shifts are reported in ppm relative to residual $CHCl_3$ (^{1}H, δ = 7.26), $CDCl_3$ (^{13}C, δ = 77.17) and residual DMSO-d_5 (^{1}H, 2.50 ppm), DMSO-d_6 (^{13}C, 39.52 ppm) as internal standards. All ^{13}C NMR spectra were proton-decoupled. Spectra ^{1}H and ^{1}H-^{13}C HSQCnd (Heteronuclear Single Quantum Coherence without ^{13}C-decoupling during ^{1}H-acquisition time) of mixture compounds **5** and **6** (Figures S23 and S24 in the SI, respectively) were recorded on Bruker DPX-300 spectrometer (300.13 MHz for ^{1}H and 75.468 MHz for ^{13}C), which was equipped a normal forward dual probe-head. In 2D HSQC experiment, relaxation delay d1 was equal to 3 s and delay for coherence transfer during evolution period d2 = 1/[4$^1J_{C,H}$)] was equal to 1.72 ms. This value corresponds to scalar constant $^1J_{C,H}$ = 145 Hz. IR spectra were obtained in KBr and wavelengths are reported in cm^{-1}. Mass spectra were recorded on a HRMS-ESI-QTOF mass-analyzer, electrospray ionization, positive mode. A single-crystal X-ray diffraction experiments for compound **8a** was carried out using Agilent Technologies Xcalibur diffractometer with monochromated MoKα radiation. Melting points were determined on a melting point apparatus and are uncorrected. Cyclopropenes **3a–j** were synthesized according to known procedures[31–36] while α-amino acids **2** and ninhydrin (**1**) were obtained from commercial sources.

One-Pot Three-Component Reaction of Ninhydrin, Sarcosine, and Cyclopropenes; General Procedure A (GP-A)

A mixture of ninhydrin (**1**; 71 mg, 0.4 mmol), sarcosine (**2**; 53 mg, 0.6 mmol) and the respective cyclopropene derivative **3a–i** (0.4 mmol) was stirred at reflux in MeOH (10 mL) for 5 h (the progress of the reaction was monitored by TLC). Upon completion, the reaction mixture was cooled to RT and the solvent was removed under reduced pressure. After evaporation of the solvent, the resulting crude material was purified by PTLC on silica gel (hexane–EtOAc 3:1), subsequent trituration with a mixture of MeOH–H_2O (2:1) afforded the corresponding pure products **4a–i**. In all cases by-product **5** was also isolated in 10–17% yields.

Two-Component Reaction of Spiroaziridine and Cyclopropenes; General Procedure B (GP-B)

A mixture of cyclopropene **3a**,**c**,**f**,**h**,**i** (0.4 mmol) and aziridine **6** as a mixture with **5** (110 mg, 0.4 mmol, the mass fraction of aziridine 67%) was stirred at reflux in MeOH (5 mL) for 3 h (progress of the reaction was monitored by TLC). The solvent was evaporated under reduced pressure. The residue was purified by PTLC on a silica gel eluting with a mixture of hexane–EtOAc (3:1 or 2:1) to afford pure products **4**.

(±)-(1*R*,5*S*,6*R*)-3-Methyl-1,5,6-triphenyl-3-azaspiro[bicyclo-[3.1.0]hexane-2,2′-indene]-1′,3′-dione (4a)

Product **4a** was obtained as a single diastereomer by following GP-A from ninhydrin (**1**; 71 mg, 0.4 mmol), sarcosine (**2**; 53 mg, 0.6 mmol), and cyclopropene **3a** (107 mg, 0.4 mmol).

Product **4a** was obtained as a single diastereomer by following GP-B from aziridine **6** (110 mg, 0.4 mmol, 67% purity) and cyclopropene **3a** (107 mg, 0.4 mmol).

Yield: GP-A – 129 mg (71%), GP-B – 135 mg (74%); yellow solid; mp 192–193 °C; R_f = 0.43 (SiO_2; hexane–EtOAc 3:1).

IR (KBr): 3303, 3093, 3070, 3034, 2941, 2892, 1746, 1731, 1707, 1599, 1495, 1270, 1170, 1115, 722, 700 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 7.0 Hz, 1 H), 7.66–7.56 (m, 3 H), 7.49–7.42 (m, 2 H), 7.30–7.16 (m, 3 H), 6.99–6.91 (m, 2 H), 6.90–6.81 (m, 3 H), 6.78–6.72 (m, 3 H), 6.48–6.42 (m, 2 H), 4.04 (s, 1 H), 3.92 (d, *J* = 9.1 Hz, 1 H), 3.62 (d, *J* = 9.1 Hz, 1 H), 2.42 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 204.9, 201.5, 142.3, 140.9, 136.6, 135.7, 135.6, 134.4, 132.7 (2 C), 132.6 (2 C), 131.5, 131.3 (2 C), 127.8 (2 C), 127.5 (2 C), 127.1, 126.9, 126.4 (2 C), 125.2, 122.4, 122.0, 80.4, 67.5, 53.1, 43.8, 35.3, 32.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{32}H_{26}NO_2^+$: 456.1958; found: 456.1958.

(±)-(1*R*,5*S*,6*R*)-6-Ethyl-3-methyl-1,5-diphenyl-3-azaspiro[bicyclo-[3.1.0]hexane-2,2′-indene]-1′,3′-dione (4b)

Product **4b** was obtained as a single diastereomer by following GP-A from ninhydrin (**1**; 71 mg, 0.4 mmol), sarcosine (**2**; 53 mg, 0.6 mmol), and cyclopropene **3b** (88 mg, 0.4 mmol); yield: 101 mg (62%); yellow solid; mp 142–143 °C; R_f = 0.53 (SiO_2; hexane–EtOAc 3:1).

IR (KBr): 3077, 3060, 2971, 2932, 2885, 1736, 1703, 1595, 1522, 1330, 1261, 1235, 774, 703 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 7.4 Hz, 1 H), 7.64 (t, *J* = 7.4 Hz, 1 H), 7.57 (t, *J* = 7.4 Hz, 1 H), 7.47 (d, *J* = 7.4 Hz, 1 H), 7.25–7.15 (m, 5 H), 6.95 (d, *J* = 7.4 Hz, 2 H), 6.90–6.86 (m, 3 H), 3.94 (d, *J* = 8.6 Hz, 1 H), 3.69 (d, *J* = 8.6 Hz, 1 H), 2.70 (dd, *J* = 7.9, 6.1 Hz, 1 H), 2.36 (s, 3 H), 1.49 (m, 1 H), 1.20 (m, 1 H), 0.91 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 204.3, 202.0, 142.1, 140.9, 137.6, 135.6, 135.3, 132.3 (2 C), 132.2, 129.3 (2 C), 127.6 (2 C), 127.5 (2 C), 127.0, 125.8, 122.3, 121.9, 80.3, 63.5, 50.2, 38.6, 35.3, 30.9, 19.2, 13.8.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{28}H_{25}NO_2Na^+$: 430.1778; found: 430.1777.

(±)-(1*R*,5*S*,6*R*)-3-Methyl-1,5-diphenyl-6-vinyl-3-azaspiro[bicyclo-[3.1.0]hexane-2,2′-indene]-1′,3′-dione (4c)

Product **4c** was obtained as a single diastereomer by following GP-A from ninhydrin (**1**; 71 mg, 0.4 mmol), sarcosine (**2**; 53 mg, 0.6 mmol), and cyclopropene **3c** (87 mg, 0.4 mmol).

Product **4c** was obtained as a single diastereomer by following GP-B from aziridine **6** (110 mg, 0.4 mmol, 67% purity) and cyclopropene **3c** (87 mg, 0.4 mmol).

Yield: GP-A – 96 mg (59%), GP-B – 114 mg (70%); yellow solid; mp 156–157 °C; R_f = 0.48 (SiO_2; hexane–EtOAc 3:1).

IR (KBr): 3070, 3030, 3020, 2935, 2875, 2844, 2800, 1735, 1703, 1596, 1262, 1235, 1181, 909, 772, 732, 706 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (d, *J* = 7.5 Hz, 1 H), 7.67–7.54 (m, 5 H), 7.33–7.27 (m, 2 H), 7.23–7.17 (m, 1 H), 7.06–7.00 (m, 2 H), 6.86–6.79 (m, 3 H), 5.50 (dd, *J* = 16.0, 4.0 Hz, 1 H), 5.09–4.96 (m, 2 H), 3.87 (d, *J* = 8.9 Hz, 1 H), 3.58–3.51 (m, 2 H), 2.35 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 204.9, 201.5, 142.4, 141.1, 136.8, 136.4, 135.9, 135.7, 132.5 (2 C), 131.6 (2 C), 128.1 (3 C), 127.8 (2 C), 127.2, 127.0, 122.6, 122.1, 115.1, 80.2, 66.0, 51.0, 42.1, 35.4, 32.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{24}NO_2^+$: 406.1802; found: 406.1807.

(±)-(1*R*,5*S*,6*R*)-3-Methyl-1,5-diphenyl-6-(phenylethynyl)-3-azaspiro[bicyclo[3.1.0]hexane-2,2′-indene]-1′,3′-dione (4d)

Product **4d** was obtained as a single diastereomer by following GP-A from ninhydrin (**1**; 71 mg, 0.4 mmol), sarcosine (**2**; 53 mg, 0.6 mmol), and cyclopropene **3d** (117 mg, 0.4 mmol); yield: 129 mg (67%); yellow solid; mp 182–183 °C; R_f = 0.42 (SiO_2; hexane–EtOAc 3:1).

IR (KBr): 3081, 3057, 3048, 2974, 2946, 2929, 2890, 2843, 2225, 1740, 1705, 1592, 1490, 1445, 1346, 1268, 1231, 894, 772, 759, 701 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 7.4 Hz, 1 H), 7.68 (t, *J* = 7.4 Hz, 1 H), 7.62 (t, *J* = 7.4 Hz, 1 H), 7.56 (d, *J* = 7.4 Hz, 1 H), 7.53 (d, *J* = 7.6 Hz, 2 H), 7.30–7.20 (m, 3 H), 7.20–7.05 (m, 7 H), 6.95–6.90 (m, 3 H), 4.14 (d, *J* = 8.6 Hz, 1 H), 3.84 (s, 1 H), 3.89 (d, *J* = 8.6 Hz, 1 H), 2.41 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 203.7, 200.4, 142.0, 140.9, 135.9, 135.6, 135.2, 132.6 (2 C), 131.2 (2 C), 130.7, 129.9 (2 C), 128.0 (2 C), 127.5 (3 C), 127.4 (3 C), 126.6, 123.8, 122.5, 122.1, 87.3, 87.0, 79.3, 62.3, 51.7, 41.6, 35.1, 20.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{34}H_{26}NO_2^+$: 480.1958; found: 480.1968.

(±)-(1*R*,5*S*)-3-Methyl-1,5-diphenyl-3-azaspiro[bicyclo[3.1.0]hexane-2,2′-indene]-1′,3′-dione (4e)

Product **4e** was obtained by following GP-A from ninhydrin (**1**; 71 mg, 0.4 mmol), sarcosine (**2**; 53 mg, 0.6 mmol), and cyclopropene **3e** (77 mg, 0.4 mmol); yield: 103 mg (68%); yellow solid; mp 187–189 °C; R_f = 0.44 (SiO_2; hexane–EtOAc 3:1).

IR (KBr): 3018, 2934, 2835, 2799, 1739, 1704, 1594, 1503, 1446, 1348, 1272, 1231, 1176, 1074, 1018, 895, 769, 705, 610, 522 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.81 (d, *J* = 7.4 Hz, 1 H), 7.63 (t, *J* = 7.4 Hz, 1 H), 7.58 (t, *J* = 7.4 Hz, 1 H), 7.55 (d, *J* = 7.4 Hz, 1 H), 7.28 (d, *J* = 7.7 Hz, 2 H), 7.21 (t, *J* = 7.7 Hz, 2 H), 7.12 (t, *J* = 7.7 Hz, 1 H), 6.89 (d, *J* = 7.7 Hz, 2 H), 6.83–6.78 (m, 3 H), 4.14 (d, *J* = 8.7 Hz, 1 H), 3.49 (d, *J* = 8.7 Hz, 1 H), 2.63 (d, *J* = 4.8 Hz, 1 H), 2.38 (s, 3 H), 1.50 (d, *J* = 4.8 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 204.7, 200.9, 141.8, 140.9, 137.7, 135.7, 135.5, 134.5, 131.7 (2 C), 128.4 (2 C), 128.0 (2 C), 127.5 (2 C), 127.1, 126.4, 122.5, 121.9, 79.5, 61.4, 48.5, 36.5, 35.4, 19.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{21}NO_2Na^+$: 402.1465; found: 402.1463.

Methyl (±)-(1*R*,5*S*,6*R*)-3-Methyl-1′,3′-dioxo-1,5-diphenyl-1′,3′-dihydro-3-azaspiro[bicyclo[3.1.0]hexane-2,2′-indene]-6-carboxylate (4f)

Product **4f** was obtained as a single diastereomer by following GP-A from ninhydrin (**1**; 71 mg, 0.4 mmol), sarcosine (**2**; 53 mg, 0.6 mmol), and cyclopropene **3f** (100 mg, 0.4 mmol).

Product **4f** was obtained as a single diastereomer by following GP-B from aziridine **6** (110 mg, 0.4 mmol, 67% purity) and cyclopropene **3f** (100 mg, 0.4 mmol).

Yield: GP-A – 89 mg (51%), GP-B – 110 mg (63%); yellow solid; mp 185–186 °C; R_f = 0.42 (SiO_2; hexane–EtOAc 2:1).

IR (KBr): 3049, 2964, 2940, 2894, 2845, 2801, 1736, 1705, 1591, 1445, 1356, 1235, 1200, 1178, 901, 769, 707 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 7.4 Hz, 1 H), 7.70–7.55 (m, 3 H), 7.53–7.47 (m, 2 H), 7.35–7.27 (m, 2 H), 7.27–7.19 (m, 1 H), 7.06–6.97 (m, 2 H), 6.90–6.79 (m, 3 H), 3.87 (d, *J* = 9.3 Hz, 1 H), 3.79 (s, 1 H), 3.58 (d, *J* = 9.3 Hz, 1 H), 3.49 (s, 3 H), 2.32 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 203.8, 200.3, 169.7, 142.4, 141.0, 136.2, 136.0, 134.1, 131.5, 131.3 (2 C), 130.9 (2 C), 128.1 (2 C), 127.7 (2 C), 127.5, 127.4, 122.8, 122.3, 79.6, 65.9, 52.8, 51.6, 44.6, 35.2, 29.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{24}NO_4^+$: 438.1700; found: 438.1686.

(±)-(1*R*,5*S*,6*R*)-*N*-Isopropyl-3-methyl-1′,3′-dioxo-1,5-diphenyl-1′,3′-dihydro-3-azaspiro[bicyclo[3.1.0]hexane-2,2′-indene]-6-carboxamide (4g)

Product **4g** was obtained as a single diastereomer by following GP-A from ninhydrin (**1**; 71 mg, 0.4 mmol), sarcosine (**2**; 53 mg, 0.6 mmol), and cyclopropene **3g** (111 mg, 0.4 mmol); yield: 113 mg (61%); yellow solid; mp 195–197 °C; R_f = 0.55 (SiO_2; hexane–EtOAc 1:1).

IR (KBr): 3327, 3059, 3030, 2969, 2934, 2866, 2844, 2793, 1741, 1707, 1643, 1539, 1230, 768, 702 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 7.4 Hz, 1 H), 7.67 (t, *J* = 7.4 Hz, 1 H), 7.61 (t, *J* = 7.4 Hz, 1 H), 7.58 (d, *J* = 7.7 Hz, 2 H), 7.55 (d, *J* = 7.4 Hz, 1 H), 7.30 (t, *J* = 7.7 Hz, 2 H), 7.22 (t, *J* = 7.7 Hz, 1 H), 7.09–7.04 (m, 2 H), 6.86–6.81 (m, 3 H), 4.90 (d, *J* = 7.6 Hz, 1 H), 3.84 (d, *J* = 9.2 Hz, 1 H), 3.81–3.77 (m, 1 H), 3.52 (d, *J* = 9.2 Hz, 1 H), 3.48 (s, 1 H), 2.29 (s, 3 H), 0.84 (d, *J* = 6.5 Hz, 3 H), 0.78 (d, *J* = 6.5 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 204.1, 201.0, 166.9, 142.2, 140.8, 135.9, 135.7, 134.2, 131.5 (2 C), 131.4, 131.2 (2 C), 127.7 (2 C), 127.6 (2 C), 127.5, 127.1, 122.5, 122.0, 79.5, 65.9, 51.4, 42.9, 41.1, 34.9, 31.3, 22.2, 22.1

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{30}H_{28}N_2O_3Na^+$: 487.1992; found: 487.1990.

(±)-(1*R*,5*S*,6*R*)-*N*,*N*,3-Trimethyl-1′,3′-dioxo-1,5-diphenyl-1′,3′-dihydro-3-azaspiro[bicyclo[3.1.0]hexane-2,2′-indene]-6-carboxamide (4h)

Product **4h** was obtained as a single diastereomer by following GP-A from ninhydrin (**1**; 71 mg, 0.4 mmol), sarcosine (**2**; 53 mg, 0.6 mmol), and cyclopropene **3h** (105 mg, 0.4 mmol).

Product **4h** was obtained as a single diastereomer by following GP-B from aziridine **6** (110 mg, 0.4 mmol, 67% purity) and cyclopropene **3h** (105 mg, 0.4 mmol).

Yield: GP-A – 114 mg (63%), GP-B – 119 mg (66%); yellow solid; mp 218–219 °C; R_f = 0.33 (SiO_2; hexane–EtOAc 2:1).

IR (KBr): 3048, 3020, 2935, 2880, 2845, 2805, 1742, 1707, 1647, 1598, 1448, 1261, 1241, 1151, 1072, 768, 703 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.88–7.80 (m, 1 H), 7.71–7.66 (m, 1 H), 7.62–7.56 (m, 1 H), 7.44–7.36 (m, 1 H), 7.23–7.10 (m, 5 H), 7.00–6.90 (m, 2 H), 6.87–6.75 (m, 3 H), 4.13 (d, *J* = 8.9 Hz, 1 H), 3.80 (s, 1 H), 3.68 (d, *J* = 8.9 Hz, 1 H), 2.97 (s, 3 H), 2.69 (s, 3 H), 2.38 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 203.2, 200.6, 167.9, 142.2, 141.0, 135.8, 135.5, 135.4, 133.0 (2 C), 130.0, 128.8 (2 C), 127.5 (2 C), 127.1, 126.7 (2 C), 126.4, 122.4, 122.0, 80.4, 61.8, 51.8, 40.0, 37.1, 35.2 (2 C), 30.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{29}H_{27}N_2O_3^+$: 451.2016; found: 451.2025.

(±)-(1*R*,5*S*,6*R*)-3-Methyl-1′,3′-dioxo-1,5-diphenyl-1′,3′-dihydro-3-azaspiro[bicyclo[3.1.0]hexane-2,2′-indene]-6-carbonitrile (4i)

Product **4i** was obtained as a single diastereomer by following GP-A from ninhydrin (**1**; 71 mg, 0.4 mmol), sarcosine (**2**; 53 mg, 0.6 mmol), and cyclopropene **3i** (87 mg, 0.4 mmol).

Product **4i** was obtained as a single diastereomer by following GP-B from aziridine **6** (110 mg, 0.4 mmol, 67% purity) and cyclopropene **3i** (87 mg, 0.4 mmol).

Yield: GP-A – 99 mg (61%), GP-B – 110 mg (68%); yellow solid; mp 189–190 °C; R_f = 0.37 (SiO_2; hexane–EtOAc 2:1).

IR (KBr): 3070, 3048, 2948, 2886, 2839, 2800, 2238, 1741, 1704, 1597, 1265, 1242, 770, 760, 704 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 7.4 Hz, 1 H), 7.73–7.61 (m, 2 H), 7.60–7.56 (m, 1 H), 7.55–7.49 (m, 2 H), 7.37–7.30 (m, 2 H), 7.30–7.24 (m, 1 H), 7.12–7.04 (m, 2 H), 7.01–6.91 (m, 3 H), 4.04 (d, *J* = 9.4 Hz, 1 H), 3.73 (s, 1 H), 3.58 (d, *J* = 9.4 Hz, 1 H), 2.33 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.8, 199.0, 141.9, 140.7, 136.4, 136.2, 132.8, 131.8 (2 C), 129.6 (2 C), 128.9, 128.6, 128.4 (2 C), 128.3 (2 C), 127.9, 122.9, 122.4, 118.0, 77.9, 62.3, 50.7, 41.7, 34.9, 15.9.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{27}H_{21}N_2O_2Na^+$: 427.1417; found: 427.1399.

Mixture of 1-Methylspiro[aziridine-2,2′-indene]-1′,3′-dione (6) and 1′,4′-Dimethyldispiro[indene-2,2′-piperazine-5′,2″-indene]-1,1″,3,3″-tetrone (5)

A mixture of ninhydrin (**1**; 500 mg, 2.8 mmol) and sarcosine (**2**; 250 mg, 2.8 mmol) was stirred at RT in MeOH (5 mL) for 72 h. The resulting light brown solid was collected by filtration and washed with cold MeOH to afford **6** and **5** as an inseparable mixture in 4:1 ratio, respectively (the ratio was established by means of ^{1}H NMR spectroscopy); yield: 240 mg (46%); light brown solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ (for **6**) = 7.70–7.80 (m, 4 H), 3.45 (s, 2 H), 2.24 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (for **6**) = 198.5 (2 C), 140.9 (2 C), 136.4 (2 C), 122.9 (2 C), 71.9, 49.1, 40.6.

On heating the mixture of **5** and **6** in MeOH, aziridine **6** completely converted into dispiropiperazine **5**. The spectral data for **5** are in good accordance with previously published data (Figures S19 and S20 in the SI).[27]

One-Pot Three-Component Reaction of Ninhydrin, Primary α-Amino Acids, and Cyclopropenes; General Procedure C (GP-C)

A mixture of ninhydrin (**1**; 71 mg, 0.4 mmol), cyclopropene **3** (0.4 mmol), and α-amino acid **7** (0.8 mmol) in a 3:1 mixture of MeOH–H_2O (12 mL) was refluxed for 10 h. The reaction progress was monitored by TLC and by the change in the color of the reaction mixture from blue to yellow. The solvent was evaporated under reduced pressure. The residue was subjected by silica gel PTLC using a mixture of hexane–EtOAc as an eluent. Subsequent trituration with a mixture of MeOH–H_2O (2:1) gave desired products **8** and **9**.

(±)-(1*R*,4*R*,5*S*,6*R*)-4-Isobutyl-1,5,6-triphenyl-3-azaspiro[bicyclo-[3.1.0]hexane-2,2′-indene]-1′,3′-dione (8a)[37]

The reaction was performed according to GP-C employing ninhydrin (**1**; 71 mg, 0.4 mmol), cyclopropene **3a** (107 mg, 0.4 mmol), and L-leucine (**7a**; 105 mg, 0.8 mmol). Purification by PTLC on silica gel (hexane–EtOAc, 3:1) followed by trituration with a mixture of MeOH–H_2O (2:1) afforded **8a** as a single diastereomer; yield: 147 mg (74%); yellow solid; mp 171–172 °C; R_f = 0.37 (SiO_2, hexane–EtOAc 3:1).

IR (KBr): 3300, 2998, 2960, 2887, 1743, 1710, 1598, 1495, 1267, 937, 762, 719, 700 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85–7.73 (m, 1 H), 7.70–7.55 (m, 3 H), 7.39 (d, *J* = 7.2 Hz, 2 H), 7.33–7.18 (m, 3 H), 7.00 (t, *J* = 7.2 Hz, 1 H), 6.91 (t, *J* = 7.5 Hz, 2 H), 6.85–6.68 (m, 5 H), 6.45 (d, *J* = 7.5 Hz, 2 H), 4.39 (d, *J* = 8.1 Hz, 1 H), 3.27 (s, 1 H), 2.48 (br s, 1 H), 1.78–1.63 (m, 1 H), 1.56–1.44 (m, 1 H), 1.40–1.27 (m, 1 H), 0.90 (s, 3 H), 0.80 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.3, 200.2, 141.7, 136.2, 135.8, 135.3, 134.0, 132.8 (3 C), 132.6 (2 C), 131.6, 131.2 (2 C), 127.8 (2 C), 127.5, 126.8 (3 C), 126.5 (2 C), 125.3, 122.9, 122.7, 77.4, 69.6, 53.2, 49.6, 39.9, 28.1, 25.7, 23.8, 21.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{35}H_{32}NO_2^+$: 498.2428; found: 498.2438.

(±)-(1*R*,4*R*,5*S*,6*R*)-1,5,6-Triphenyl-4-propyl-3-azaspiro[bicyclo-[3.1.0]hexane-2,2′-indene]-1′,3′-dione (8b)

The reaction was performed according to GP-C employing ninhydrin (**1**; 71 mg, 0.4 mmol), cyclopropene **3a** (107 mg, 0.4 mmol), and DL-norvaline (**7b**; 94 mg, 0.8 mmol). Purification by PTLC on silica gel (hexane–EtOAc 3:1) followed by trituration with a mixture of MeOH–H_2O (2:1) afforded **8b** as a single diastereomer; yield: 137 mg (71%); yellow solid; mp 104–105 °C; R_f = 0.36 (SiO_2, hexane–EtOAc 3:1).

IR (KBr): 3056, 3027, 2957, 2930, 1745, 1600, 1496, 1267, 765, 702 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84–7.76 (m, 1 H), 7.69–7.52 (m, 3 H), 7.43–7.20 (m, 5 H), 7.05–6.60 (m, 8 H), 6.49–6.35 (m, 2 H), 4.41–4.35 (m, 1 H), 3.33 (s, 1 H), 2.19 (br s, 1 H), 1.69–1.17 (m, 4 H), 0.91–0.85 (m, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.1, 199.7, 141.7 (2 C), 136.0, 135.9, 135.4, 134.0, 132.8 (3 C), 132.6 (2 C) 131.3, 131.2 (2 C), 127.8 (2 C), 127.6, 126.9 (2 C), 126.5 (2 C), 125.4, 123.0, 122.7, 77.4, 71.3, 53.0, 49.2, 32.9, 28.3, 20.3, 14.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{34}H_{30}NO_2^+$: 484.2271; found: 484.2268.

(±)-(1*R*,4*R*,5*S*,6*R*)-4-Butyl-1,5,6-triphenyl-3-azaspiro[bicyclo-[3.1.0]hexane-2,2′-indene]-1′,3′-dione (8c)

The reaction was performed according to GP-C employing ninhydrin (**1**; 71 mg, 0.4 mmol), cyclopropene **3a** (107 mg, 0.4 mmol), and DL-norleucine (**7c**; 105 mg, 0.8 mmol). Purification by PTLC on silica gel (hexane–EtOAc 3:1) followed by trituration with a mixture of MeOH–H_2O (2:1) afforded **8c** as a single diastereomer; yield: 163 mg (81%); yellow solid; mp 95–96 °C; R_f = 0.38 (SiO_2, hexane–EtOAc, 3:1).

IR (KBr): 3305, 3027, 2954, 2929, 1745, 1601, 1497, 1445, 1267, 764, 701 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 7.2 Hz, 1 H), 7.71–7.53 (m, 3 H), 7.44–7.34 (m, 2 H), 7.33–7.17 (m, 3 H), 7.00 (t, *J* = 7.1 Hz, 1 H), 6.90 (t, *J* = 7.2 Hz, 2 H), 6.84–6.61 (m, 5 H), 6.52–6.37 (m, 2 H), 4.45–4.29 (m, 1 H), 3.34 (s, 1 H), 2.19 (br s, 1 H), 1.68–1.17 (m, 6 H), 0.92–0.71 (m, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.3, 200.0, 141.7 (2 C), 136.1, 135.8, 135.3, 134.1, 132.8 (3 C), 132.6 (2 C), 131.5, 131.2 (2 C), 127.8 (2 C), 127.5, 126.9, 126.8, 126.5 (2 C), 125.3, 122.9, 122.7, 77.2, 71.5, 53.2, 49.4, 30.6, 29.3, 28.2, 22.9, 13.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{35}H_{32}NO_2^+$: 498.2428; found: 498.2427.

(±)-(1*R*,4*R*,5*S*,6*R*)-4-Hexyl-1,5,6-triphenyl-3-azaspiro[bicyclo-[3.1.0]hexane-2,2'-indene]-1',3'-dione (8d)

The reaction was performed according to GP-C employing ninhydrin (**1**; 71 mg, 0.4 mmol), cyclopropene **3a** (107 mg, 0.4 mmol), and DL-2-aminocaprylic acid (**7d**; 127 mg, 0.8 mmol). Purification by PTLC on silica gel (hexane–EtOAc, 3:1) followed by trituration with a mixture of MeOH–H_2O (2:1) afforded **8d** as a single diastereomer; yield: 151 mg (72%); yellow solid; mp 149–150 °C; R_f = 0.43 (SiO_2, hexane–EtOAc 3:1).

IR (KBr): 3297, 2940, 2889, 2855, 1745, 1596, 1495, 1354, 1268, 938, 723, 698 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 7.3 Hz, 1 H), 7.68–7.56 (m, 3 H), 7.39 (d, *J* = 6.7 Hz, 2 H), 7.33–7.19 (m, 3 H), 7.00 (t, *J* = 7.2 Hz, 1 H), 6.95–6.87 (m, 2 H), 6.84–6.64 (m, 5 H), 6.45 (d, *J* = 7.5 Hz, 2 H), 4.41–4.27 (m, 1 H), 3.31 (s, 1 H), 2.19 (br s, 1 H), 1.65–1.05 (m, 10 H), 0.85 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.2, 199.9, 141.7 (2 C), 136.1, 135.8, 135.4, 134.0, 133.9, 132.8 (2 C), 132.6, 131.5, 131.4, 131.2 (2 C), 127.8 (2 C), 127.6, 126.9 (2 C), 126.5 (2 C), 125.4, 123.0, 122.7, 77.3, 71.6, 53.1, 49.4, 31.7, 30.9, 29.5, 28.2, 27.1, 22.5, 14.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{37}H_{36}NO_2^+$: 526.2741; found: 526.2744.

(±)-(1*R*,4*R*,5*S*,6*R*)-4-Benzyl-1,5,6-triphenyl-3-azaspiro[bicyclo-[3.1.0]hexane-2,2′-indene]-1′,3′-dione (8e)

The reaction was performed according to GP-C employing ninhydrin (**1**; 71 mg, 0.4 mmol), cyclopropene **3a** (107 mg, 0.4 mmol), and L-phenylalanine (**7e**; 132 mg, 0.8 mmol). Purification by PTLC on silica gel (hexane–EtOAc 2:1) followed by trituration with a mixture of MeOH–H_2O (2:1) afforded **8e** as a single diastereomer; yield: 168 mg (79%); off-white solid; mp 192–193 °C; R_f = 0.59 (SiO_2, hexane–EtOAc, 2:1).

IR (KBr): 3426, 3059, 3026, 2921, 1740, 1600, 1493, 1445, 1276, 753, 699 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79–7.73 (m, 1 H), 7.65–7.56 (m, 3 H), 7.47 (d, *J* = 7.5 Hz, 2 H), 7.35–7.19 (m, 8 H), 7.02 (t, *J* = 7.2 Hz, 1 H), 6.95–6.86 (m, 2 H), 6.85–6.65 (m, 5 H), 6.41 (d, *J* = 7.5 Hz, 2 H), 4.72 (dd, *J* = 8.8, 3.7 Hz, 1 H), 3.32 (s, 1 H), 2.99 (dd, *J* = 14.3, 3.7 Hz, 1 H), 2.80 (dd, *J* = 14.5, 8.9 Hz, 1 H), 2.61 (br s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.1, 199.5, 141.5 (2 C), 138.0 (2 C), 135.7 (2 C), 133.6, 132.8 (2 C), 132.4, 131.2 (2 C), 131.1, 129.0 (2 C), 128.4 (2 C), 127.8 (3 C), 127.4 (2 C), 126.9, 126.8, 126.4 (2 C), 126.3, 125.3, 122.8, 122.5, 77.4, 71.2, 52.3, 48.3, 36.3, 28.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{38}H_{30}NO_2^+$: 532.2271; found: 532.2296.

(±)-(1*R*,4*R*,5*S*,6*R*)-4-(4-Hydroxybenzyl)-1,5,6-triphenyl-3-azaspiro[bicyclo[3.1.0]hexane-2,2′-indene]-1′,3′-dione (8f)

The reaction was performed according to GP-C employing ninhydrin (**1**; 71 mg, 0.4 mmol), cyclopropene **3a** (107 mg, 0.4 mmol), and L-tyrosine (**7f**; 145 mg, 0.8 mmol). Purification by PTLC on silica gel (hexane–EtOAc 3:2) followed by trituration with a mixture of MeOH–H_2O (2:1) afforded **8f** as a single diastereomer; yield: 136 mg (62%); off-white solid; mp 234–235 °C; R_f = 0.38 (SiO_2, hexane–EtOAc 3:2).

IR (KBr): 3526, 3202, 3065, 3011, 2902, 1740, 1702, 1590, 1514, 1492, 1446, 1362, 1330, 1246, 1085, 1031, 755, 690 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.11 (s, 1 H), 7.81–7.70 (m, 3 H), 7.60 (d, *J* = 6.7 Hz, 1 H), 7.38–7.24 (m, 5 H), 7.02–6.75 (m, 10 H), 6.61 (d, *J* = 8.1 Hz, 2 H), 6.35 (d, *J* = 8.1 Hz, 2 H), 4.58 (dd, *J* = 8.7, 3.6 Hz, 1 H), 3.38 (s, 1 H), 2.80 (dd, *J* = 14.1, 3.6 Hz, 1 H), 2.65 (dd, *J* = 14.3, 9.1 Hz, 1 H), 2.47 (br s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 203.9, 200.6, 156.0, 141.6, 141.1, 137.0, 136.8, 136.5, 134.7, 132.8 (2 C), 132.4 (2 C), 132.1, 131.2 (2 C), 130.2 (2 C), 129.7, 128.4 (2 C), 128.0 (2 C), 127.4 (2 C), 126.9 (2 C), 125.7, 122.9, 122.8, 115.4 (2 C), 75.8, 71.5, 51.3, 48.1, 35.5, 28.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{38}H_{30}NO_3^+$: 548.2220; found: 548.2229.

(±)-(1*R*,4*R*,5*S*,6*R*)-4-(4-Hydroxy-3,5-diiodobenzyl)-1,5,6-triphenyl-3-azaspiro[bicyclo[3.1.0]hexane-2,2′-indene]-1′,3″-dione (8g)

The reaction was performed according to GP-C employing ninhydrin (**1**; 71 mg, 0.4 mmol), cyclopropene **3a** (107 mg, 0.4 mmol), and 3,5-diiodo-L-tyrosine (**8g**; 346 mg, 0.8 mmol). Purification by PTLC on silica gel (hexane–EtOAc 2:1) followed by trituration with a mixture of MeOH–H_2O (2:1) afforded **8g** as a single diastereomer; yield: 182 mg (57%); yellow solid; mp 205–206 °C; R_f = 0.43 (SiO_2, hexane–EtOAc, 2:1).

IR (KBr): 3481, 3308, 3027, 2886, 1742, 1702, 1599, 1465, 1268, 1155, 701 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81–7.76 (m, 1 H), 7.68–7.55 (m, 3 H), 7.48 (s, 2 H), 7.40–7.36 (m, 2 H), 7.34–7.21 (m, 3 H), 7.05–7.00 (m, 1 H), 6.95–6.90 (m, 2 H), 6.87–6.64 (m, 5 H), 6.44 (d, *J* = 7.3 Hz, 2 H), 5.67 (br s, 1 H), 4.58 (dd, *J* = 9.0, 4.2 Hz, 1 H), 3.89 (s, 1 H), 2.81 (dd, *J* = 14.4, 4.2 Hz, 1 H), 2.65 (dd, *J* = 14.4, 9.0 Hz, 1 H). 2.18 (br s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.8, 199.9, 152.5, 142.0, 141.8, 139.8 (2 C), 136.3, 136.0, 135.9, 134.9, 133.8, 133.2 (2 C), 132.9 (2 C), 131.6 (2 C), 131.4, 128.4 (2 C), 128.0 (2 C), 127.6, 127.4, 127.0 (2 C), 125.9, 123.3, 123.2, 82.7 (2 C), 76.9, 71.8, 53.1, 48.8, 35.5, 28.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{38}H_{28}I_2NO_3^+$: 800.0153; found: 800.0161.

(±)-(1*R*,4*R*,5*S*,6*R*)-4-[2-(Methylthio)ethyl]-1,5,6-triphenyl-3-azaspiro[bicyclo[3.1.0]hexane-2,2′-indene]-1′,3′-dione (8h)

The reaction was performed according to GP-C employing ninhydrin (**1**; 71 mg, 0.4 mmol), cyclopropene **3a** (107 mg, 0.4 mmol), and L-methionine (**7h**; 119 mg, 0.8 mmol). Purification by PTLC on silica gel (hexane–EtOAc 3:1) followed by trituration with a mixture of MeOH–H_2O (2:1) afforded **8h** as a single diastereomer; yield: 151 mg (73%); light yellow solid; mp 175–177 °C; R_f = 0.32 (SiO_2, hexane–EtOAc 5:2).

IR (KBr): 3304, 3025, 2913, 1745, 1705, 1599, 1496, 1443, 1352, 1269, 1183, 1153, 1099, 1028, 942, 910, 837, 754, 704, 623 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85–7.75 (m, 1 H), 7.71–7.56 (m, 3 H), 7.44–7.36 (m, 2 H), 7.33–7.19 (m, 3 H), 7.08–6.95 (m, 1 H), 6.94–6.86 (m, 2 H), 6.84–6.65 (m, 5 H), 6.52–6.38 (m, 2 H), 4.52–4.43 (m, 1 H), 3.35 (s, 1 H), 2.72–2.40 (m, 2 H), 2.25 (br s, 1 H), 2.07 (s, 3 H), 1.96–1.74 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.0, 199.6, 141.7, 141.6, 135.9, 135.7, 135.5, 133.6, 132.7 (2 C), 132.5 (2 C), 131.2 (2 C), 131.1 (2 C), 128.0 (2 C), 127.6, 127.1, 127.0, 126.6 (2 C), 125.5, 123.0, 122.8, 76.7, 70.6, 52.9, 48.9, 31.6, 30.5, 28.2, 15.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{34}H_{30}NO_2S^+$: 516.1992; found: 516.1997.

(±)-(1*R*,4*R*,5*S*,6*R*)-1,4,5,6-Tetraphenylspiro[3-azabicyclo[3.1.0]hexane-2,2′-indene]-1′,3′-dione (8i)

The reaction was performed according to GP-C employing ninhydrin (**1**; 71 mg, 0.4 mmol), cyclopropene **3a** (107 mg, 0.4 mmol), and DL-phenylglycine (**7i**; 121 mg, 0.8 mmol). Purification by PTLC on silica gel (hexane–EtOAc 2:1) followed by trituration with a mixture of MeOH–H_2O (2:1) afforded **8i** as a single diastereomer; yield: 145 mg (70%); yellow solid; mp 128–130 °C; R_f = 0.55 (SiO_2, hexane–EtOAc 2:1).

IR (KBr): 3342, 3028, 2886, 1741, 1708, 1598, 1494, 1285, 1262, 757, 701 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85–7.80 (m, 1 H), 7.73–7.61 (m, 3 H), 7.42–7.36 (m, 2 H), 7.34–7.17 (m, 8 H), 7.04–6.97 (m, 1 H), 6.95–6.86 (m, 2 H), 8.84–6.74 (m, 5 H), 6.47 (d, *J* = 7.3 Hz, 2 H), 5.66 (s, 1 H), 3.84 (s, 1 H), 3.49 (br s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 203.2, 199.7, 141.8, 141.4, 137.9, 135.9, 135.8, 135.6, 133.4, 133.1 (2 C), 132.7 (2 C), 131.3 (2 C), 131.2, 128.2 (2 C), 127.8, 127.6 (4 C), 127.5 (2 C), 127.1, 126.9, 126.5 (2 C), 125.5, 122.9, 122.8, 76.7, 73.6, 52.2, 49.1, 29.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{37}H_{28}NO_2^+$: 518.2115; found: 518.2121.

(±)-(1*R*,4*R*,5*S*,6*R*)-3-(1′,3′-Dioxo-1,5,6-triphenyl-1′,3′-dihydro-3-azaspiro[bicyclo[3.1.0]hexane-2,2′-indene]-4-yl)propanoic Acid (8j)

The reaction was performed according to GP-C employing ninhydrin (**1**; 71 mg, 0.4 mmol), cyclopropene **3a** (107 mg, 0.4 mmol), and L-glutamic acid (**7j**; 118 mg, 0.8 mmol). Purification by PTLC on silica gel (hexane–EtOAc 1:1) followed by trituration with a mixture of MeOH–H_2O (2:1) afforded **8j** as a single diastereomer; yield: 127 mg (62%); yellow solid; mp 204–205 °C; R_f = 0.37 (SiO_2, hexane–EtOAc 1:1).

IR (KBr): 3306, 3015, 2950, 1745, 1708, 1600, 1496, 1443, 1351, 1270, 1187, 756, 720, 701 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.96 (br s, 1 H), 7.87–7.34 (m, 3 H), 7.73–7.63 (m, 1 H), 7.38–7.18 (m, 5 H), 7.03–6.94 (m, 1 H), 6.94–6.86 (m, 2 H), 6.83–6.73 (m, 5 H), 6.35 (d, *J* = 7.3 Hz, 2 H), 4.20–4.05 (m, 1 H), 3.76–3.68 (m, 1 H), 3.61 (s, 1 H), 2.37–2.20 (m, 1 H), 2.20–2.01 (m, 1 H), 1.84–1.66 (m, 1 H), 1.65–1.47 (m, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 203.6, 200.5, 174.8, 141.6, 141.0, 137.0, 136.9, 136.7, 134.6, 132.7 (2 C), 132.4 (2 C), 132.1, 131.1 (2 C), 130.2, 128.3 (2 C), 128.0 (2 C), 127.5, 127.4, 126.9 (2 C), 125.7, 123.0, 76.0, 69.4, 51.7, 48.3, 31.6, 28.2, 26.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{34}H_{28}NO_4^+$: 514.2013; found: 514.2027.

(±)-(1*R*,4*R*,5*S*,6*R*)-4-Isobutyl-1,5-diphenyl-6-(phenylethynyl)-3-azaspiro[bicyclo[3.1.0]hexane-2,2′-indene]-1′,3′-dione (8k)

The reaction was performed according to GP-C employing ninhydrin (**1**; 71 mg, 0.4 mmol), cyclopropene **3d** (117 mg, 0.4 mmol), and L-leucine (**7a**; 105 mg, 0.8 mmol). Purification by PTLC on silica gel (hexane–EtOAc 3:1) followed by trituration with a mixture of MeOH–H_2O (2:1) afforded **8k** as a single diastereomer; yield: 144 mg (69%); light yellow solid; mp 157–158 °C; R_f = 0.51 (SiO_2, hexane–EtOAc 5:2).

IR (KBr): 3298, 3087, 3078, 3056, 3027, 2956, 2927, 2905, 2869, 2223, 1745, 1712, 1599, 1491, 1447, 1418, 1346, 1328, 1270, 1192, 1157, 1077, 1020, 945, 755, 694 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90–7.83 (m, 3 H), 7.68–7.58 (m, 3 H), 7.33 (t, *J* = 7.4 Hz, 2 H), 7.22 (t, *J* = 7.4 Hz, 1 H), 7.17–7.10 (m, 5 H), 7.03 (d, *J* = 7.4 Hz, 2 H), 6.88–6.80 (m, 3 H), 4.44 (t, *J* = 6.3 Hz, 1 H), 3.03 (s, 1 H), 2.23 (br s, 1 H), 1.68 (m, 1 H), 1.48–1.42 (m, 2 H), 0.87 (d, *J* = 6.6 Hz, 3 H), 0.85 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 201.6, 199.5, 141.5 (2 C), 136.0, 135.5, 135.0, 132.1 (2 C), 131.5, 131.2 (2 C), 131.1 (2 C), 127.9 (2 C), 127.8 (2 C), 127.5, 127.4 (2 C), 127.1, 126.9, 123.7, 123.0, 122.9, 87.7, 87.1, 76.3, 67.2, 52.3, 49.0, 40.4, 25.7, 23.6, 21.8, 14.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{37}H_{32}NO_2^+$: 522.2428; found: 522.2438.

(±)-(1*R*,4*R*,5*S*)-4-Isobutyl-1,5-diphenyl-3-azaspiro[bicyclo-[3.1.0]hexane-2,2′-indene]-1′,3′-dione (8l)

The reaction was performed according to GP-C employing ninhydrin (**1**; 71 mg, 0.4 mmol), cyclopropene **3e** (77 mg, 0.4 mmol), and L-leucine (**7a**; 105 mg, 0.8 mmol). Purification by PTLC on silica gel (hexane–EtOAc 3:1) followed by trituration with a mixture of MeOH–H_2O (2:1) afforded **8l** as a single diastereomer; yield: 128 mg (76%); light yellow solid; mp 130–132 °C; R_f = 0.54 (SiO_2, hexane–EtOAc 5:2).

IR (KBr): 3316, 3027, 2956, 2912, 1744, 1709, 1598, 1497, 1447, 1348, 1274, 1194, 1151, 1078, 771, 707 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (d, *J* = 7.4 Hz, 1 H), 7.64–7.56 (m, 3 H), 7.42 (d, *J* = 7.6 Hz, 2 H), 7.25 (t, *J* = 7.6 Hz, 2 H), 7.14 (t, 1 H), 6.90 (d, *J* = 7.4 Hz, 2 H), 6.80–6.76 (m, 3 H), 4.61 (t, *J* = 6.5 Hz, 1 H), 2.10 (br s, 1 H), 2.00 (d, *J* = 6.1 Hz, 1 H), 1.68 (m, 1 H), 1.44 (d, *J* = 6.1 Hz, 1 H), 1.42–1.57 (m, 2 H), 0.90 (d, *J* = 6.6 Hz, 3 H), 0.86 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.5, 199.8, 141.6, 137.3, 135.8, 135.3, 134.9, 131.5 (3 C), 129.2 (2 C), 128.2 (2 C), 127.5 (2 C), 126.9, 126.6, 122.9, 122.8, 76.6, 64.3, 48.8, 43.8, 41.1, 25.6, 23.5, 22.1, 13.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{29}H_{27}NO_2Na^+$: 444.1934; found: 444.1932.

(±)-(1*R*,4*R*,5*S*,6*R*)-4-Isobutyl-*N*-isopropyl-1′,3′-dioxo-1,5-diphenyl-1′,3′-dihydro-3-azaspiro[bicyclo[3.1.0]hexane-2,2'-indene]-6-carboxamide (8m)

The reaction was performed according to GP-C employing ninhydrin (**1**; 71 mg, 0.4 mmol), cyclopropene **3g** (111 mg, 0.4 mmol), and L-leucine (**7a**; 105 mg, 0.8 mmol). Purification by PTLC on silica gel (hexane–EtOAc 2:1) followed by trituration with a mixture of MeOH–H_2O (2:1) afforded **8m** as a single diastereomer; yield: 130 mg (64%); light yellow solid; mp 240–242 °C; R_f = 0.31 (SiO_2, hexane–EtOAc 3:2).

IR (KBr): 3409, 3294, 3090, 3080, 3062, 3026, 2953, 2866, 1739, 1691, 1587, 1514, 1447, 1358, 1270, 1213, 1156, 1094, 760, 718, 701 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 7.4 Hz, 1 H), 7.71–7.60 (m, 5 H), 7.36 (t, *J* = 7.4 Hz, 2 H), 7.27 (t, *J* = 7.4 Hz, 1 H), 7.12–7.07 (m, 2 H), 6.90–6.85 (m, 3 H), 4.23 (dd, *J* = 10.0, 3.5 Hz, 1 H), 4.04 (d, *J* = 7.6 Hz, 1 H), 3.82–3.68 (m, 1 H), 2.83 (s, 1 H), 2.24 (br s, 1H), 1.65–1.54 (m, 1 H), 1.43 (ddd, *J* = 14.0, 10.0, 4.8 Hz, 1 H), 1.30 (ddd, , *J* = 14.0, 9.6, 3.5 Hz, 1 H), 0.83 (d, *J* = 6.5 Hz, 3 H), 0.75 (d, *J* = 6.5 Hz, 3 H), 0.66 (d, *J* = 6.5 Hz, 3 H), 0.51 (d, *J* = 6.5 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 201.3, 199.4, 167.1, 141.7, 141.5, 136.0, 135.6, 133.4, 132.0 (2 C), 131.5, 131.4 (2 C), 128.1 (2 C), 128.0 (2 C), 127.6, 127.5, 123.0, 122.9, 76.3, 69.1, 51.0, 49.4, 41.0, 39.6, 27.6, 25.6, 23.6, 21.9, 21.8, 21.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{33}H_{35}N_2O_3^+$: 507.2642; found: 507.2638.

(±)-(1*R*,4*R*,5*S*,6*R*)-4-Isobutyl-1′,3′-dioxo-1,5-diphenyl-1′,3′-dihydro-3-azaspiro[bicyclo[3.1.0]hexane-2,2′-indene]-6-carboxylic Acid (9a)

The reaction was performed according to GP-C employing ninhydrin (**1**; 71 mg, 0.4 mmol), cyclopropene **3j** (94 mg, 0.4 mmol), and L-leucine (**7a**; 105 mg, 0.8 mmol). Purification by PTLC on silica gel (hexane–EtOAc 1:1) followed by trituration with a mixture of MeOH–H_2O (2:1) afforded **9a** as a single diastereomer; yield: 127 mg (68%); white solid; mp >260 °C; R_f = 0.56 (SiO_2, hexane–EtOAc 1:1).

IR (KBr): 3270, 3090, 3081, 2990, 2984, 2535, 1749, 1678, 1602, 1402, 1345, 1328, 1288, 1265, 1192, 1009, 755, 719, 696 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.08 (br s, 1 H), 7.89–7.77 (m, 3 H), 7.68 (d, J = 6.9 Hz, 1 H), 7.47 (d, J = 7.6 Hz, 2 H), 7.37 (t, J = 7.5 Hz, 2 H), 7.27 (t, J = 7.3 Hz, 1 H), 7.00–6.92 (m, 2 H), 6.92–6.80 (m, 3 H), 4.22–4.11 (m, 1 H), 3.55 (br s, 1 H), 3.17 (s, 1 H), 1.60–1.37 (m, 2 H), 1.08–0.96 (m, 1 H), 0.80 (d, J = 6.4 Hz, 3 H), 0.66 (d, J = 6.4 Hz, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 203.3, 200.0, 141.6, 141.0, 137.0, 136.7, 134.9, 132.9, 131.6 (2 C), 131.1 (2 C), 128.2 (2 C), 127.7 (2 C), 127.3, 127.2, 123.1, 123.0, 75.5, 67.1, 40.6, 39.5, 39.4, 25.2 (2 C), 24.1, 21.7.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{30}H_{28}NO_4^+$: 466.2013; found: 466.2020.

(±)-(1*R*,4*R*,5*S*,6*R*)-4-Butyl-1′,3′-dioxo-1,5-diphenyl-1′,3′-dihydro-3-azaspiro[bicyclo[3.1.0]hexane-2,2′-indene]-6-carboxylic Acid (9b)

The reaction was performed according to GP-C employing ninhydrin (**1**; 71 mg, 0.4 mmol), cyclopropene **3j** (94 mg, 0.4 mmol), and DL-norleucine (**7c**; 105 mg, 0.8 mmol). Purification by PTLC on silica gel (hexane–EtOAc 1:1) followed by trituration with a mixture of MeOH–H_2O (2:1) afforded **9b** as a single diastereomer; yield: 95 mg (51%); beige solid; mp >260 °C; R_f = 0.60 (SiO_2, hexane–EtOAc 1:1).

IR (KBr): 3262, 3090, 3065, 3028, 2955, 2931, 2871, 2693, 2526, 1746, 1721, 1588, 1496, 1449, 1208, 1186, 870, 754, 710 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.03 (br s, 1 H), 7.90–7.75 (m, 3 H), 7.67 (d, J = 6.9 Hz, 1 H), 7.47 (d, J = 7.3 Hz, 2 H), 7.37 (t, J = 7.5 Hz, 2 H), 7.26 (t, J = 7.5 Hz, 1 H), 7.02–6.93 (m, 2 H), 6.92–6.80 (m, 3 H), 4.13–4.00 (m, 1 H), 3.60 (br s, 1 H), 3.19 (s, 1 H), 1.48–0.97 (m, 6 H), 0.75 (t, J = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 203.4, 200.1, 170.9, 141.6, 141.0, 137.0, 136.7, 135.1, 132.9, 131.6 (2 C), 131.1 (2 C), 128.2 (2 C), 127.7 (2 C), 127.3, 127.2, 123.1, 123.0, 75.4, 69.0, 51.8, 49.9, 30.2, 29.0, 25.3, 22.6, 14.3.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{30}H_{28}NO_4^+$: 466.2013; found: 466.2023.

(±)-(1*R*,4*R*,5*S*,6*R*)-4-Hexyl-1′,3′-dioxo-1,5-diphenyl-1′,3′-dihydro-3-azaspiro[bicyclo[3.1.0]hexane-2,2′-indene]-6-carboxylic Acid (9c)

The reaction was performed according to GP-C employing ninhydrin (**1**; 71 mg, 0.4 mmol), cyclopropene **3j** (94 mg, 0.4 mmol), and DL-2-aminocaprylic acid (**7d**; 127 mg, 0.8 mmol). Purification by PTLC on silica gel (hexane–EtOAc 1:1) followed by trituration with a mixture of MeOH–H_2O (2:1) afforded **9c** as a single diastereomer; yield: 83 mg (42%); beige solid; mp 205–207 °C; R_f = 0.66 (SiO_2, hexane–EtOAc 1:1).

IR (KBr): 3262, 3059, 3025, 2955, 2929, 2859, 2515, 1750, 1713, 1679, 1264, 723, 705 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.06 (br s, 1 H), 7.90–7.75 (m, 3 H), 7.66 (d, J = 7.2 Hz, 1 H), 7.46 (d, J = 7.5 Hz, 2 H), 7.37 (t, J = 7.6 Hz, 2 H), 7.26 (t, J = 7.2 Hz, 1 H), 6.97–6.92 (m, 2 H), 6.91–6.80 (m, 3 H), 4.08–4.03 (m, 1 H), 3.76 (br s, 1 H), 3.18 (s, 1 H), 1.31–1.08 (m, 10 H), 0.80 (t, J = 6.7 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 203.4, 200.1, 170.9, 141.6, 141.0, 137.0, 136.8, 135.0, 132.9, 131.6 (2 C), 131.1 (2 C), 128.2 (2 C), 127.7 (2 C), 127.3, 127.2, 123.1, 123.0, 75.4, 69.0, 51.8, 49.9, 31.6, 30.6, 29.2, 26.7, 25.3, 24.6, 22.4.

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{32}H_{31}NO_4^+$Na: 516.2145; found: 516.2148.

(±)-(1*R*,4*R*,5*S*,6*R*)-1′,3′-Dioxo-1,4,5-triphenyl-1′,3′-dihydro-3-azaspiro[bicyclo[3.1.0]hexane-2,2′-inden]-6-carboxylic Acid (9d)

The reaction was performed according to GP-C employing ninhydrin (**1**; 71 mg, 0.4 mmol), cyclopropene **3j** (94 mg, 0.4 mmol), and DL-phenylglycine (**7i**; 121 mg, 0.8 mmol). Purification by PTLC on silica gel (hexane–EtOAc 1:1) followed by trituration with a mixture of MeOH–H_2O (2:1) afforded **9d** as a single diastereomer; yield: 118 mg (61%); white solid; mp 250–251 °C; R_f = 0.53 (SiO_2, hexane–EtOAc 1:1).

IR (KBr): 3263, 3000, 2723, 2500, 1727, 1706, 1590, 1498, 1447, 1354, 1196, 1000, 752, 695 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.58 (br s, 1 H), 7.90–7.76 (m, 3 H), 7.67 (d, J = 7.5 Hz, 1 H), 7.41–7.22 (m, 8 H), 7.08–6.98 (m, 4 H), 6.94–6.82 (m, 3 H), 5.37 (d, J = 4.9 Hz, 1 H), 4.14 (d, J = 4.9 Hz, 1 H), 3.58 (s, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 205.0, 200.2, 170.7, 141.7, 140.9, 139.3, 136.8, 137.6, 134.4, 132.7, 132.0 (2 C), 131.2 (2 C), 128.3 (2 C), 128.1, 128.0 (2 C), 127.8 (2 C), 127.5 (3 C), 127.4, 123.0, 122.8, 74.7, 70.7, 51.2, 50.4, 25.7.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{32}H_{24}NO_4^+$: 486.1700; found: 486.1706.

(±)-(1*R*,4*R*,5*S*,6*R*)-4-Benzyl-1′,3′-dioxo-1,5-diphenyl-1′,3′-dihydro-3-azaspiro[bicyclo[3.1.0]hexane-2,2′-indene]-6-carboxylic Acid (9e)

The reaction was performed according to GP-C employing ninhydrin (**1**; 71 mg, 0.4 mmol), cyclopropene **3j** (94 mg, 0.4 mmol, and L-phenylalanine (**7e**; 132 mg, 0.8 mmol). Purification by PTLC on silica gel (hexane–EtOAc 1:1) followed by trituration with a mixture of MeOH–H_2O (2:1) afforded **9e** as a single diastereomer; yield: 78 mg (39%); off-white solid; mp 238–239 °C; R_f = 0.52 (SiO_2, hexane–EtOAc 1:1).

IR (KBr): 3432, 3262, 3055, 2929, 2684, 2510, 1732, 1706, 1497, 1448, 1415, 1379, 1269, 1198, 1017, 855, 729, 698 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.15 (br s, 1 H), 7.82 (d, J = 7.2 Hz, 1 H), 7.78 (t, J = 7.2 Hz, 1 H), 7.74 (t, J = 7.2 Hz, 1 H), 7.59 (d, J = 7.2 Hz, 1 H), 7.54 (d, J = 7.4 Hz, 2 H), 7.41 (t, J = 7.4 Hz, 2 H), 7.29 (t, J = 7.4 Hz, 1 H), 7.19 (t, J = 7.7 Hz, 2 H), 7.11 (t, J = 7.7 Hz, 1 H), 7.05 (d, J = 7.7 Hz, 2 H), 6.96 (d, J = 7.4 Hz, 2 H), 6.88 (t, J = 7.4 Hz, 2 H), 6.83 (t, J = 7.4 Hz, 1 H), 4.33 (ddd, J = 9.8, 7.2, 2.6 Hz, 1 H), 3.54 (d, J = 7.2 Hz, 1 H), 3.36 (s, 1 H), 2.69 (dd, J = 13.7, 9.8 Hz, 1 H), 2.60 (dd, J = 13.7, 2.6 Hz, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 203.6, 199.9, 170.9, 141.6, 141.0, 139.7, 136.8, 136.6, 134.7, 132.7, 131.7 (2 C), 131.1 (2 C), 129.2 (2 C), 128.7 (2 C), 128.4 (2 C), 127.8 (2 C), 127.5, 127.3, 126.4, 123.0, 122.9, 75.3, 70.7, 51.6, 49.6, 36.6, 25.3.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{33}H_{26}NO_4^+$: 500.1856; found: 500.1872.

(±)-(1*R*,4*R*,5*S*,6*R*)-4-Isopropyl-1′,3′-dioxo-1,5-diphenyl-1′,3′-dihydro-3-azaspiro[bicyclo[3.1.0]hexane-2,2′-indene]-6-carboxylic Acid (9f)

The reaction was performed according to GP-C employing ninhydrin (**1**; 71 mg, 0.4 mmol), cyclopropene **3j** (94 mg, 0.4 mmol), and L-valine (**7k**; 94 mg, 0.8 mmol). Purification by PTLC on silica gel (hexane–EtOAc 1:1) followed by trituration with a mixture of MeOH–H_2O (2:1) afforded **9f** as a single diastereomer; yield: 40 mg (22%); off-white solid; mp >260 °C; R_f = 0.54 (SiO_2, hexane–EtOAc 1:1).

IR (KBr): 3445, 3260, 2905, 1725, 1595, 1494, 1430, 1339, 1281, 1202, 1155, 996, 956, 876, 823, 753, 729, 698 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.13 (br s, 1 H), 7.90–7.75 (m, 3 H), 7.61 (d, J = 7.2 Hz, 1 H), 7.55–7.48 (d, J = 7.4 Hz, 2 H), 7.41–7.29 (m, 2 H), 7.26–7.20 (m, 1 H), 6.86–6.79 (m, 5 H), 4.18 (d, J = 5.0 Hz, 1 H), 3.58 (br s, 1 H), 3.41 (s, 1 H), 1.61 (m, 1 H), 0.95 (d, J = 6.6 Hz, 3 H), 0.70 (d, J = 6.6 Hz, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 204.2, 200.5, 171.1, 141.7, 141.0, 136.8, 136.6, 135.5, 132.7, 131.6 (2 C), 131.3 (2 C), 128.2 (2 C), 127.6 (2 C), 127.2 (2 C), 122.9, 122.8, 74.3, 72.9, 50.4, 47.8, 29.7, 26.1, 21.3, 18.2.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{29}H_{26}NO_4^+$: 452.1856; found: 452.1862.

One-Pot Three-Component Reaction of Ninhydrin, Glycine Peptides, and Cyclopropenes; General Procedure D (GP-D)

A mixture of ninhydrin (**1**; 71 mg, 0.4 mmol) cyclopropene **3** (0.4 mmol) and peptide **10** (0.8 mmol) was refluxed in a mixture of MeOH–H_2O (3:1, 20 mL) in the presence of AcOH (50 μL) for 12 h (TLC control). After cooling, all volatiles were removed in vacuo and the residue was subjected to silica gel PTLC using CH_2Cl_2–MeOH as an eluent. Subsequent trituration with a mixture of MeOH–water (2:1) gave pure cycloadduct **11**.

(±)-{(1*R*,4*S*,5*S*,6*R*)-1′,3′-Dioxo-1,5,6-triphenyl-1′,3′-dihydro-3-azaspiro[bicyclo[3.1.0]hexane-2,2′-indene]-4-carbonyl}glycine (11a)

Product **11a** was obtained as a single diastereomer by following GP-D from ninhydrin (**1**; 71 mg, 0.4 mmol), cyclopropene **3a** (107 mg, 0.4 mmol), and Gly-Gly (**10a**; 106 mg, 0.8 mmol); yield: 91 mg (42%); off-white solid; mp 189–190 °C; R_f = 0.49 (SiO_2, CH_2Cl_2–MeOH, 10:1).

IR (KBr): 3381, 3376, 3053, 2501, 1743, 1707, 1625, 1601, 1532, 1266, 701 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.55 (br s, 1 H), 7.96–7.72 (m, 4 H), 7.65 (d, J = 6.9 Hz, 1 H), 7.31–7.15 (m, 5 H), 7.01–6.91 (m, 1 H), 6.92–6.62 (m, 7 H), 6.28 (d, J = 7.4 Hz, 2 H), 4.66 (d, J = 7.5 Hz, 1 H), 3.89 (d, J = 8.0 Hz, 1 H), 3.84 (s, 1 H), 3.83–3.71 (m, 1 H), 3.71–3.56 (m, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 203.1, 199.9, 169.9 (2 C), 141.6, 141.0, 137.1, 136.9, 136.2, 133.2 (2 C), 133.1 (2 C), 132.5, 131.3 (3 C), 128.0 (4 C), 127.6, 127.5, 126.8 (2 C), 125.8, 123.2, 123.1, 76.4, 71.1, 51.7, 47.6, 41.3, 28.1.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{34}H_{27}N_2O_5^+$: 543.1914; found: 543.1930.

(±)-{(1*R*,4*S*,5*S*,6*R*)-1′,3′-Dioxo-1,5,6-triphenyl-1′,3′-dihydro-3-azaspiro[bicyclo[3.1.0]hexane-2,2′-indene]-4-carbonyl}glycylglycine (11b)

Product **11b** was obtained as a single diastereomer by following GP-D from ninhydrin (**1**; 71 mg, 0.4 mmol), cyclopropene **3a** (107 mg, 0.4 mmol), and Gly-Gly-Gly (**10b**; 151 mg, 0.8 mmol); yield: 130 mg (54%); white solid; mp 167–168 °C; R_f = 0.54 (SiO_2, CH_2Cl_2–MeOH 10:1).

IR (KBr): 3327, 3040, 2935, 2500, 1741, 1709, 1665, 1529, 1498, 1266, 1220, 1045, 702 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.59 (br s, 1H), 7.97 (br s, 1 H), 7.92–7.72 (m, 4 H), 7.65 (d, J = 6.7 Hz, 1 H), 7.38–7.11 (m, 5 H), 7.07–6.56 (m, 8 H), 6.27 (d, J = 7.3 Hz, 2 H), 4.69 (d, J = 7.5 Hz, 1 H), 3.94–3.85 (m, 2 H), 3.82 (s, 1 H), 3.74 (br s, 1 H), 3.66–3.53 (m, 2 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 203.1, 199.8, 169.8 (2 C), 169.1, 141.6, 141.0, 137.1, 136.9, 136.1, 133.1, 133.0 (3 C), 132.5 (2 C), 131.2 (3 C), 128.1 (2 C), 128.0 (2 C), 127.5, 126.9 (2 C), 125.9, 123.2, 123.1, 76.4, 71.2, 51.7, 47.5, 42.3, 41.2, 28.1.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{36}H_{30}N_3O_6^+$: 600.2129; found: 600.2150.

(±)-(1*R*,4*S*,5*S*,6*R*)-4-[(Carboxymethyl)carbamoyl]-1′,3′-dioxo-1,5-diphenyl-1′,3′-dihydro-3-azaspiro[bicyclo[3.1.0]hexane-2,2′-indene]-6-carboxylic Acid (11c)

Product **11c** was obtained as a single diastereomer by following GP-D from ninhydrin (**1**; 71 mg, 0.4 mmol), cyclopropene **3j** (94 mg, 0.4 mmol), and Gly-Gly (**10a**; 106 mg, 0.8 mmol); yield: 129 mg (63%); off-white solid; mp 207–208 °C; R_f = 0.54 (SiO_2, CH_2Cl_2–MeOH 10:1).

IR (KBr): 3378, 3064, 1743, 1707, 1622, 1533, 1432, 1287, 1265, 1228, 1190, 953, 701 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.20 (br s, 1 H), 7.90 (d, J = 7.3 Hz, 1 H), 7.88–7.76 (m, 3 H), 7.65 (s, J = 7.3 Hz, 1 H), 7.44 (d, J = 7.3 Hz, 2 H), 7.32 (t, J = 7.3 Hz, 2 H), 7.23 (t, J = 7.2 Hz, 1 H), 7.02–6.80 (m, 5 H), 4.58 (d, J = 8.0 Hz, 1 H), 3.72–3.57 (m, 2 H), 3.37 (s, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 202.4, 199.2, 170.2, 169.4 (2 C), 141.5, 141.0, 137.3, 137.0, 133.2, 132.1 (2 C), 132.0, 131.2 (2 C), 127.9 (4 C), 127.5, 127.4, 123.3, 123.2, 76.0, 70.6, 52.2, 48.8, 41.4, 25.1.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{29}H_{23}N_2O_7^+$: 511.1500; found: 511.1512.

(±)-4-({2-[(Carboxymethyl)amino]-2-oxoethyl}carbamoyl)-1′,3′-dioxo-1,5-diphenyl-1′,3′-dihydro-3-azaspiro[bicyclo[3.1.0]hexane-2,2′-indene]-6-carboxylic Acid (11d)

Product **11d** was obtained as a single diastereomer by following GP-D from ninhydrin (**1**; 71 mg, 0.4 mmol), cyclopropene **3j** (94 mg, 0.4 mmol), and Gly-Gly-Gly (**10b**; 151 mg, 0.8 mmol); yield: 114 mg (50%); off-white solid; mp 194–195 °C; R_f = 0.42 (SiO_2, CH_2Cl_2–MeOH 10:1).

IR (KBr): 3326, 3059, 2960, 1741, 1669, 1533, 1413, 1266, 1196, 700 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.20 (br s, 2 H), 7.95 (br s, 1 H), 7.93–7.73 (m, 4 H), 7.65 (d, J = 7.4 Hz, 1 H), 7.48–7.40 (m, 2 H), 7.38–7.30 (m, 2 H), 7.26–7.20 (m, 1 H), 7.01–6.80 (m, 5 H), 4.61 (d, J = 8.0 Hz, 1 H), 3.91–3.54 (m, 5 H), 3.36 (s, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 202.5, 199.2, 170.1, 169.3 (2 C), 169.0, 141.5, 140.9, 137.3, 137.0, 133.4, 132.0 (3 C), 131.2 (2 C), 128.0 (2 C), 127.9 (2 C), 127.5 (2 C), 123.3, 123.2, 76.0, 70.7, 52.2, 48.7, 42.4, 41.2, 25.2.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{31}H_{26}N_3O_8^+$: 568.1714; found: 568.1727.

Computational Methodology

The full geometry optimization of reactants, products, and transition states structures (TSs) were carried out at DFT/HF level of theory using M11 hybrid exchange-correlation functional[38] and cc-pVDZ basis set.[39] The polarizable continuum model (PCM) was used to calculate solvent effects of MeOH.[40] The optimizations were performed using the Berny analytical gradient optimization method.[41] All stationary points were described by harmonic vibrational frequency calculations to prove the location of correct minima (only real frequencies) and transition states (only one imaginary frequency). For the transition states, the normal modes corresponding to the imaginary frequencies were related to the vibrations of new developing bonds. IRC

calculations were conducted to check the energy profiles connecting each TS to the two associated minima of the proposed mechanism.[42] Thermal corrections to enthalpy and entropy values were evaluated at 298.15 K and 1.0 atm. All calculations were performed using Gaussian 09 computational program package.[43]

Bioassay Details

Tumor Cell Line

The cervical carcinoma (HeLa) cell line was obtained from the Bank of Cell Cultures of the Institute of Cytology of the Russian Academy of Sciences. HeLa cells were cultured in the DMEM medium (Thermo scientific, USA) with the addition of 10% fetal calf serum (FCS) (Thermo scientific, USA) and 40 μg/mL gentamicin (Sigma, USA).

MTS Assay

A colorimetric MTS assay was used for assessing cell metabolic activity. This method in based on the reduction of 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2*H*-tetrazolium (MTS) to colored and soluble in cell culture media formazan product by NAD(P)H-dependent dehydrogenase enzymes. Since this conversion and such decrease of MTS can only occur in metabolically active cells, the level of activity is the measure of the viability of the cells. Shortly, cells were seeded in a 96-well microtiter plates at a density of 100×10^3 cells per well in 100 μL of complete medium and allowed to grow and adhere onto the wells during 24 h at 37 °C. After that the cells were treated with various concentrations of the compounds for a period of 24 or 72 h. After the treatment, 20 μL of MTS reagent was added into each well and incubated at 37 °C for 2 h. Finally, the absorbance was recorded at 490 nm using 96-well plate reader 'Multiskan GO' (Thermo Fisher Scientific, USA). For colored solutions the protocol was modified as followed: the absorbance was recorded directly before the addition of MTS reagent and measured values were further subtracted from final absorbance.

Statistical Analysis

Significance of results was performed using Student's *t*-test. Statistical processing of results was performed using Origin Pro software. IC_{50} was calculated using Prism 6 for Windows. Differences between groups were considered significant at $p \leq 0.05$.

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Supporting Information

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References

(1) (a) Liu, H.-W.; Walsh, C. T. In *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; Wiley: New York, **1987**, 959–1025. (b) Netz, N.; Opatz, T. *J. Org. Chem.* **2016**, *81*, 1723.

(2) (a) Moffat, D.; Patel, S.; Day, F.; Belfield, A.; Donald, A.; Rowlands, M.; Wibawa, J.; Brotherton, D.; Stimson, L.; Clark, V.; Owen, J.; Bawden, L.; Box, G.; Bone, E.; Mortenson, P.; Hardcastle, A.; Meurs, S.; Eccles, S.; Raynaud, F.; Aherne, W. *J. Med. Chem.* **2010**, *53*, 8663. (b) Lunn, G.; Banks, B. J.; Crook, R.; Feeder, N.; Pettman, A.; Sabnis, Y. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4608. (c) McHardy, S. F.; Heck, S. D.; Guediche, S.; Kalman, M.; Allen, M. P.; Tu, M.; Bryce, D. K.; Schmidt, A. W.; Vanase-Frawley, M.; Callegari, E.; Doran, S.; Grahame, N. J.; Mclean, S.; Liras, S. *Med. Chem. Commun.* **2011**, *2*, 1001. (d) Orri, M.; Abraham, L.; Giraldi, A. *J. Sex. Med.* **2013**, *10*, 2484.

(3) (a) Li, T.; Liang, J.; Ambrogelly, A.; Brennan, T.; Gloor, G.; Huisman, G.; Lalonde, J.; Lekhal, A.; Mijts, B.; Muley, S.; Newman, L.; Tobin, M.; Wong, G.; Zaks, A.; Zhang, X. *J. Am.Chem. Soc.* **2012**, *134*, 6467. (b) Topczewski, J. J.; Cabrera, P. J.; Saper, N. I.; Sanford, M. S. *Nature* **2016**, *531*, 220.

(4) Micheli, F.; Cavanni, P.; Arban, R.; Benedetti, R.; Bertani, B.; Bettati, M.; Bettelini, L.; Bonanomi, G.; Braggio, S.; Checchia, A.; Davalli, S.; Di-Fabio, R.; Fazzolari, E.; Fontana, S.; Marchioro, C.; Minick, D.; Negri, M.; Oliosi, B.; Read, K. D.; Sartori, I.; Tedesco, G.; Tarsi, L.; Terreni, S.; Visentini, F.; Zocchi, A.; Zonzini, L. *J. Med. Chem.* **2010**, *53*, 2534.

(5) Micheli, F.; Arista, L.; Bonanomi, G.; Blaney, F. E.; Braggio, S.; Capelli, A. M.; Checchia, A.; Damiani, F.; Di-Fabio, R.; Fontana, S.; Gentile, G.; Griffante, C.; Hamprecht, D.; Marchioro, C.; Mugnaini, M.; Piner, J.; Ratti, E.; Tedesco, G.; Tarsi, L.; Terreni, S.; Worby, A.; Ashby, C. R. Jr.; Heidbreder, C. *J. Med. Chem.* **2010**, *53*, 374.

(6) Micheli, F.; Arista, L.; Bertani, B.; Braggio, S.; Capelli, A. M.; Cremonesi, S.; Di Fabio, R.; Gelardi, G.; Gentile, G.; Marchioro, C.; Pasquarello, A.; Provera, S.; Tedesco, G.; Tarsi, L.; Terreni, S.; Worby, A. *Heidbreder C.* **2010**, *53*, 7129.

(7) Bonanomi, G.; Braggio, S.; Capelli, A. M.; Checchia, A.; Di Fabio, R.; Marchioro, C.; Tarsi, L.; Tedesco, G.; Terreni, S.; Worby, A.; Heibreder, C.; Micheli, F. *ChemMedChem* **2010**, *5*, 705.

(8) Patel, S.; Meilandt, W. J.; Erickson, R. I.; Chen, J.; Deshmukh, G.; Estrada, A. A.; Fuji, R. N.; Gibbons, P.; Gustafson, A.; Harris, S. F.; Imperio, J.; Liu, W.; Liu, X.; Liu, Y.; Lyssikatos, J. P.; Ma, C.; Yin, J.; Lewcock, J. W.; Siu, M. *J. Med. Chem.* **2017**, *60*, 8083.

(9) Siu, M.; Ghosh, A. S.; Lewcock, J. W. *J. Med. Chem.* **2018**, *61*, 8078.

(10) McAllister, L. A.; Butler, C. R.; Mente, S.; O'Neil, S. V.; Fonseca, K. R.; Piro, J. R.; Cianfrogna, J. A.; Foley, T. L.; Gilbert, A. M.; Harris, A. R.; Helal, C. J.; Johnson, D. S.; Montgomery, J. I.; Nason, D. M.; Noell, S.; Pandit, J.; Rogers, B. N.; Samad, T. A.; Shaffer, C. L.; da Silva, R. G.; Uccello, D. P.; Webb, D.; Brodney, M. A. *J. Med. Chem.* **2018**, *61*, 3008.

(11) Velázquez, F.; Sannigrahi, M.; Bennett, B.; Lovey, R. G.; Arasappan, A.; Bogen, S.; Nair, L.; Venkatraman, S.; Blackman, M.; Hendrata, S.; Huang, Y.; Huelgas, R.; Pinto, P.; Cheng, K.-C.; Tong, X.; McPhail, A. T.; Njoroge, F. G. *J. Med. Chem.* **2010**, *53*, 3075.

(12) Jones, S.; Ahmet, J.; Ayton, K.; Ball, M.; Cockerill, M.; Fairweather, E.; Hamilton, N.; Harper, P.; Hitchin, J.; Jordan, A.; Levy, C.; Lopez, R.; McKenzie, E.; Packer, M.; Plant, D.; Simpson, L.; Simpson, P.; Sinclair, L.; Somervaille, T. C. P.; Small, H.; Spencer, G. J.; Thomson, G.; Tonge, M.; Waddell, L.; Walsh, J.; Waszkowycz, B.; Wigglesworth, M.; Wiseman, D. H.; Ogilvie, D. *J. Med. Chem.* **2016**, *59*, 11120.
(13) Nirogi, R.; Mohammed, A. R.; Shinde, A. K.; Gagginapally, S. R.; Kancharla, D. M.; Middekadi, V. R.; Bogaraju, N.; Ravella, S. R.; Singh, P.; Birangal, S. R.; Subramanian, R.; Palacharla, R. C.; Benade, V.; Muddana, N.; Jayarajan, P. *J. Med. Chem.* **2018**, *61*, 4993.
(14) Li, X.; Zhang, Z.; Chen, Y.; Wan, H.; Sun, J.; Wang, B.; Feng, B.; Hu, B.; Shi, X.; Feng, J.; Zhang, L.; He, F.; Bai, C.; Zhang, L.; Tao, W. *ACS Med. Chem. Lett.* **2019**, *10*, 996.
(15) Scott, J. S.; Barton, P.; Bennett, S. N. L.; deSchoolmeester, J.; Godfrey, L.; Kilgour, E.; Mayers, R. M.; Packer, M. J.; Rees, A.; Schofield, P.; Selmi, N.; Swales, J. G.; Whittamore, P. R. O. *Med. Chem. Commun.* **2012**, *3*, 1264.
(16) Sabbatini, F. M.; Melotto, S.; Bernasconi, G.; Bromidge, S. M.; D'Adamo, L.; Rinaldi, M.; Savoia, C.; Mundi, C.; Di Francesco, C.; Zonzini, L.; Costantini, V. J. A.; Perini, B.; Valerio, E.; Pozzan, A.; Perdonà, E.; Visentini, F.; Corsi, M.; Di Fabio, R. *ChemMedChem* **2011**, *6*, 1981.
(17) Zheng, Y.; Yu, X.; Lv, S.; Mykhailiuk, P. K.; Ma, Q.; Hai, L.; Wu, Y. *RSC Adv.* **2018**, *8*, 5114.
(18) Chen, P.; Zhu, C.; Zhu, R.; Lin, Z.; Wu, W.; Jiang, H. *Org. Biomol. Chem.* **2017**, *15*, 1228.
(19) Böhmer, J.; Grigg, R.; Marchbank, J. D. *Chem. Commun.* **2002**, 768.
(20) (a) Ohno, H.; Takeoka, Y.; Miyamura, K.; Kadoh, Y.; Tanaka, T. *Org. Lett.* **2003**, *5*, 4763. (b) Ohno, H.; Takeoka, Y.; Kadoh, Y.; Miyamura, K.; Tanaka, T. *J. Org. Chem.* **2004**, *69*, 4541.
(21) Pedroni, J.; Cramer, N. *J. Am. Chem. Soc.* **2017**, *139*, 12398.
(22) Veeranna, K. D.; Das, K. K.; Baskaran, S. *Chem. Commun.* **2019**, *55*, 7647.
(23) Wang, K.-B.; Ran, R.-Q.; Xiu, S.-D.; Li, C.-Y. *Org. Lett.* **2013**, *15*, 2374.
(24) (a) Yuan, Y.; Zheng, Z.-J.; Ye, F.; Ma, J.-H.; Xu, Z.; Bai, X.-F.; Li, L.; Xu, L.-W. *Org. Chem. Front.* **2018**, *5*, 2759. (b) Deng, H.; Yang, W.-L.; Tian, F.; Tang, W.; Deng, W.-P. *Org. Lett.* **2018**, *20*, 4121. (c) Filatov, A. S.; Knyazev, N. A.; Molchanov, A. P.; Panikorovsky, T. L.; Kostikov, R. R.; Larina, A. G.; Boitsov, V. M.; Stepakov, A. V. *J. Org. Chem.* **2017**, *82*, 959. (d) Filatov, A. S.; Knyazev, N. A.; Ryazantsev, M. N.; Suslonov, V. V.; Larina, A. G.; Molchanov, A. P.; Kostikov, R. R.; Boitsov, V. M.; Stepakov, A. V. *Org. Chem. Front.* **2018**, *5*, 595. (e) Filatov, A. S.; Knyazev, N. A.; Shmakov, S. V.; Bogdanov, A. A.; Ryazantsev, M. N.; Shtyrov, A. A.; Starova, G. L.; Molchanov, A. P.; Larina, A. G.; Boitsov, V. M.; Stepakov, A. V. *Synthesis* **2019**, *51*, 713.
(25) (a) Zimnitskiy, N. S.; Denikaev, A. D.; Barkov, A. Y.; Kutyashev, I. B.; Korotaev, V. Y.; Sosnovskikh, V. Y. *J. Org. Chem.* **2020**, *85*, 8683. (b) Kutyashev, I. B.; Barkov, A. Y.; Zimnitskiy, N. S.; Korotaev, V. Y.; Sosnovskikh, V. Y. *Chem. Heterocycl. Comp.* **2019**, *55*, 861. (c) Angyal, A.; Demjén, A.; Harmat, V.; Wölfling, J.; Puskás, L. G.; Kanizsai, I. *J. Org. Chem.* **2019**, *84*, 4273. (d) Kumaran, S.; Saritha, R.; Gurumurthy, P.; Parthasarathy, K. *Eur. J. Org. Chem.* **2020**, 2725. (e) Prabhakaran, P.; Rajakumar, P. *RSC Adv.* **2020**, *10*, 10263. (f) Gupta, S.; Khurana, J. M. *Chemistry-Select* **2019**, *4*, 7200.
(26) Filatov, A. S.; Wang, S.; Khoroshilova, O. V.; Lozovskiy, S. V.; Larina, A. G.; Boitsov, V. M.; Stepakov, A. V. *J. Org. Chem.* **2019**, *84*, 7017.
(27) Panja, S. K.; Karmakar, P.; Chakraborty, J.; Ghosh, T.; Bandyopadhyay, C. *Tetrahedron Lett.* **2008**, *49*, 4397.
(28) (a) Beletskii, E. V.; Kuznetsov, M. A. *Russ. J. Org. Chem.* **2009**, *45*, 1229. (b) Pankova, A. S.; Kuznetsov, M. A. *Tetrahedron Lett.* **2014**, *55*, 2499.
(29) Aly, M. F.; Ardill, H.; Grigg, R.; Leong-Ling, S.; Rajviroongit, S.; Surendrakumar, S. *Tetrahedron Lett.* **1987**, *28*, 6077.
(30) Nirmala, S.; Kamala, E. T. S.; Sudha, L.; Ramesh, E.; Raghunathan, R. *Anal. Sci.: X-Ray Struct. Anal. Online* **2008**, *24*, x101.
(31) Breslow, R.; Chang, H. W. *J. Am. Chem. Soc.* **1961**, *83*, 2367.
(32) Padwa, A.; Blacklock, T. J.; Getman, D.; Hatanaka, N.; Loza, R. *J. Org. Chem.* **1978**, *43*, 1481.
(33) Gilbertson, R. D.; Weakley, T. J. R.; Haley, M. M. *J. Org. Chem.* **2000**, *65*, 1422.
(34) D'yakonov, I. A.; Komendantov, M. I.; Gokhmanova, I.; Kostikov, R. R. *Russ. J. Gen. Chem.* **1958**, *29*, 3848.
(35) White, E. H.; Winter, R. E. K.; Graeve, R.; Zirngibl, U.; Friend, E. W.; Maskill, H.; Mende, U.; Kreiling, G.; Reisenauer, H. P.; Maier, G. *Chem. Ber.* **1981**, *114*, 3906.
(36) Li, H.; Praveen Rao, P. N.; Habeeb, A. G.; Knaus, E. E. *Drug Dev. Res.* **2002**, *57*, 6.
(37) Crystallographic data for compound **8a** have been deposited at the Cambridge Crystallographic Data Centre (Deposition No. CCDC-1840079) and can be obtained free of charge via www.ccdc.cam.ac.uk/structures
(38) Peveratti, R.; Truhlar, D. G. *J. Phys. Chem. Lett.* **2011**, *2*, 2810.
(39) Dunning, T. H. *J. Chem. Phys.* **1989**, *90*, 1007.
(40) Cossi, M.; Rega, N.; Scalmani, G.; Barone, V. *J. Comput. Chem.* **2003**, *24*, 669.
(41) Schlegel, H. B. *J. Comput. Chem.* **1982**, *3*, 214.
(42) Fukui, K. J. *J. Phys. Chem.* **1970**, *74*, 4161.
(43) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, N. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ő.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09, Revision C.01*; Gaussian: Wallingford CT, **2013**.