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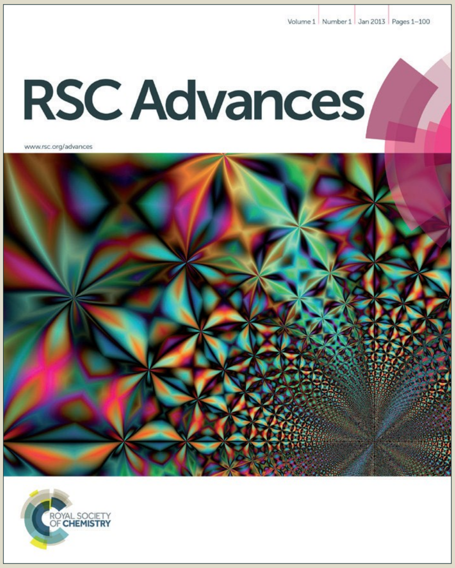

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ARTICLE

Three-component access to 2-pyrrolin-5-ones and their use in target-oriented and diversity-oriented synthesis

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The Hantzsch-type microwave-assisted, solvent-free sequential three-component reaction between primary amines, β-dicarbonyl compounds and α-bromoesters in the presence of indium trichloride afforded 2-pyrrolin-5-ones, which are difficult to access by alternative methods. Ready access to these compounds allowed their use as synthetic building blocks in a target-oriented project aimed at the synthesis of a compound that had previously been postulated as a candidate for HIV integrase inhibition on the basis of computational studies. The versatility of 2-pyrrolin-5-ones was further verified by their use in a diversity-oriented synthesis context, leading to a library of highly functionalized bispiro compounds. The overall process leading to these compounds involved the generation of six bonds and two cycles over three steps, two of which are multicomponent, and the fully controlled generation of up to four stereocenters, including two quaternary ones.

Introduction

Pyrrole is one of the most important simple heterocycles and constitutes the structural core of a large number of natural products[1] and synthetic bioactive compounds,[2] including some drugs in clinical use such as the cholesterol-lowering agent atorvastatin, the best-selling drug of all time.[3] Nevertheless, some promising pyrrole-derived simple frameworks have received very little attention because of their poor synthetic accessibility. This is the case of the 2-pyrrolin-5-one system, which has been described only a few times, and has normally been accessed by complex multistep routes in very modest yields.[4]

Multicomponent reactions (MCRs) have emerged as powerful synthetic strategies because of their efficiency, atom economy, high selectivity, and convenient construction of multiple new bonds; these characteristics give rapid access to combinatorial libraries of complex organic molecules for efficient lead structure identification and optimization in drug discovery. From the point of view of the generation of molecular diversity, the development of MCRs with a broad range of functional group tolerance are ideal because such reactions allow performing complexity-generating post-MCR transformations, such as cyclizations.[5]

In this context, it would be advantageous a synthetic efficiency perspective to devise a multicomponent approach to the 2-pyrrolin-5-one framework in order to pave the way to a deeper knowledge of its chemistry and pharmacology. Furthermore, to our knowledge such a reaction would be the first one to be described in the literature, although there is some precedent for the use of multicomponent approaches for the preparation of their conjugated isomers derived from the 2-pyrrolin-3-one skeleton.[6] Furthermore, the 2-pyrrolin-5-one thus prepared should be suitably functionalized to allow subsequent manipulation.

We envisioned that it should be possible to adapt the classical Hantzsch pyrrole synthesis[7] for our purpose. This endeavour would involve developing the three-component reaction between primary amines, α-haloesters and β-dicarbonyl compounds to furnish compounds **1**, and we describe in this article the translation of this idea into practice. A two-component process somewhat related to the one we propose here and involving the reaction of β-enamino esters with α-ketoaldehydes affords mixtures of regioisomers, giving good results only for N-hydroxyethyl or N-hydroxypropyl enamino esters, presumably because of the stabilization of the 5-oxo product by intramolecular hydrogen bonding.[8,9] A three-component variation of this reaction, starting from primary amines, α-ketoaldehydes and β-dicarbonyl compounds gives exclusively 4-hydroxypyrroles.[10]

In order to further establish the synthetic usefulness of this new method, we demonstrated its application to two situations with very different requirements, *i.e.* target-oriented and diversity-oriented synthesis (Scheme 1). For the first goal, we chose as our target compound **2**, which has been recently postulated as a candidate for HIV integrase inhibition. This proposal arose from a computational study aimed at the identification of new pharmacophores for the design of integrase inhibitors based on shape-based virtual screening of drug-like databases followed by *in silico* ADMET optimization,

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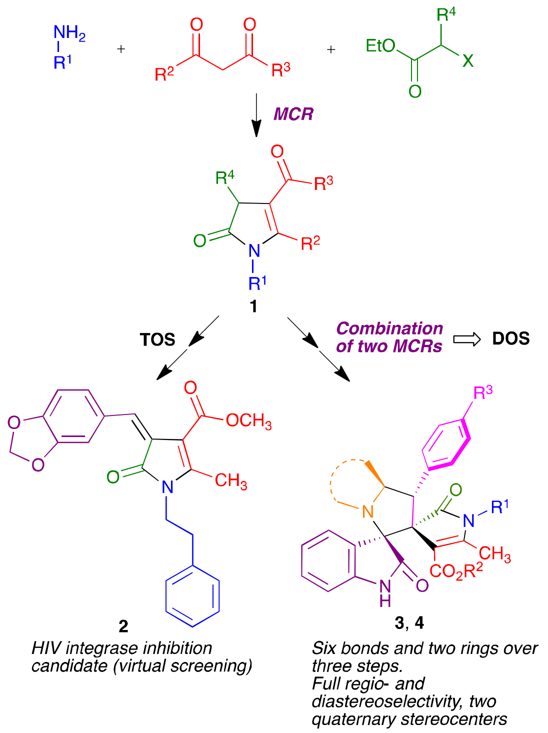
Electronic Supplementary Information (ESI) available: [copies of spectra of all compounds]. See DOI: 10.1039/x0xx00000x

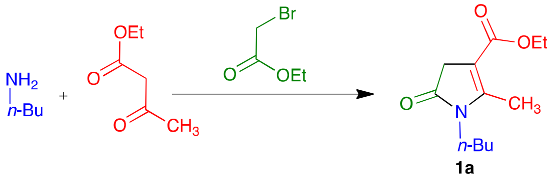


Scheme 1. Summary of the objectives of our work

QSAR predictions and docking studies.[11] Furthermore, in order to verify the possibility of generating molecular diversity from compounds **1**, we chose to study the preparation of bispiro frameworks **3** and **4** *via* the combination of our initial MCR with a second one, namely a three-component reaction involving the [3+2] dipolar cycloaddition of non-stabilized azomethine ylides with activated olefins, which offers a concise entry into functionalized spiropyrrolidine motifs with a high regio- and diastereoselectivity. The combination of two multicomponent reactions is generally recognized as an excellent approach to the generation of molecular diversity,[12,13] although it has not been widely exploited. Spirocyclic frameworks are present in many natural products and are increasingly recognized as interesting scaffolds in drug discovery programs.[14] Furthermore, spiropyrrolidine compounds are present in numerous natural products, such as (−)-horsfiline and spirotryprostatin A and have shown interesting pharmacological activities including antiproliferative[15] and antitubercular[16] properties as well as acetylcholinesterase inhibition,[17] among others. Compounds **3** and **4** have the advantage over related structures reported in the literature of the high functionalization of their pyrrolidinone moiety, which provides synthetic handles for future transformations.

Results and discussion

We started our optimization study by examining the model preparation of compound **1a** from butylamine, ethyl bromoacetate and ethyl acetoacetate (Table 1). In our first experiments, these starting materials were combined in ethanol in the presence of 5% Ce(IV) ammonium nitrate (CAN) as a Lewis acid,[18] initially at room temperature and then under reflux conditions, but no reaction was observed (entries 1 and 2). The use of focused microwave irradiation was also unsuccessful (entries 3 and 4). However, when the reaction was performed under solvent-free conditions, compound **1a** was obtained in 53% yield (entry 5), with no improvement being observed upon increase of the catalyst load (entry 6). Lanthanide triflates, represented by yttrium and ytterbium triflates, were also assayed, again with no improvement (entries 7 and 8). Boron trifluoride etherate failed to catalyze the reaction (entry 9), and aluminium trichloride gave only modest yields, even with 10% catalyst load (entries 10 and 11). Finally, indium trichloride was found to improve the results obtained with CAN, giving a 60% yield of **1a** with a 5% loading (entry 12) and almost the same result with 10% of the catalyst (entry 13). One final attempt was made using Montmorillonite K10, a clay with acidic properties that is compatible with microwave irradiation,[19] but it failed to promote our reaction (entry 14).



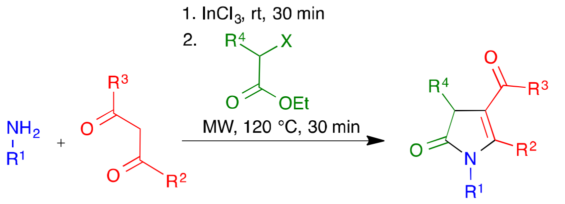
Scheme 2. Synthesis of compound **1a** from butylamine, ethyl bromoacetate and ethyl acetoacetate

Table 1. Optimization of the synthesis of compound **1a**

Entry	Catalyst (%)	Temp (°C)	Time (h)	Solvent	Yield (%)
1	CAN (5)	r.t.	20	EtOH	0^a
2	CAN (5)	80	14	EtOH	0
3	CAN (5)	80 (MW)	0.5	EtOH	0
4	CAN (5)	120 (MW)	0.5	EtOH	0
5	CAN (5)	120 (MW)	0.5	--	53
6	CAN (10)	120 (MW)	0.5	--	52
7	$Y(OTf)_3$ (5)	120 (MW)	0.5	--	50
8	$Yb(OTf)_3$ (10)	120 (MW)	0.5	--	26
9	$BF_3.Et_2O$ (10)	120 (MW)	0.5	--	Traces
10	$AlCl_3$ (5)	120 (MW)	0.5	--	19
11	$AlCl_3$ (10)	120 (MW)	0.5	--	29
12	$InCl_3$ (5)	120 (MW)	0.5	--	60
13	$InCl_3$ (10)	120 (MW)	0.5	--	58
14	Montmorillonite K10	120 (MW)	0.5	--	Traces

^{a}Using either ethyl bromoacetate or ethyl iodoacetate

These optimal conditions (5% $InCl_3$, solvent-free microwave irradiation, 120 °C) were applied to obtain a library of diversely substituted pyrrolinones in a 40-76% range of yields (Scheme 3 and Table 2), employing simple and commercially available starting materials. The scope of the R^1 substituent on nitrogen included a variety of groups such as alkyl (entries 1-4, 7-9 and 13), arylalkyl (entries 5, 6 and 12), allyl (entry 10) and functionalized alkyl (entry 11). The R^2 chain was chosen among several primary alkyl chains, including methyl, ethyl (entry 7) and propyl (entries 4 and 9). The reaction was compatible with the presence of ester or ketone functions at C-3. While most compounds **1** were unsubstituted at C-4 because our planned applications involved a condensation at this position, we also demonstrated the possibility to prepare a C_4-phenyl derivative (entry 13). In this case, the α-haloester component was an iodide, and aluminium trichloride proved to be more efficient in promoting the reaction than indium trichloride. Finally, we also examined several reactions starting from ethyl β-aminocrotonate. Thus, its reaction with ethyl 2-bromoacetate gave the N-unsubstituted pyrrolinone **1n** in 55% yield (entry 14). This is a significant result because a previous preparation of this compound by reaction of the same aminocrotonate with glyoxal required a 7-h reflux in ethanol and afforded **1n** in only 29% yield.[8] Three additional examples of N-unsubstituted pyrrolinones were obtained by the same method (entries 15-17). Interestingly, we did not observe the isomerization of 2-pyrrolyn-5-ones to their regioisomeric 4-hydroxypyrroles noticed by previous authors.[9]



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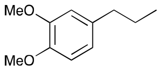
Scheme 3. Sequential multicomponent synthesis of 2-pyrrolin-5-ones **1**

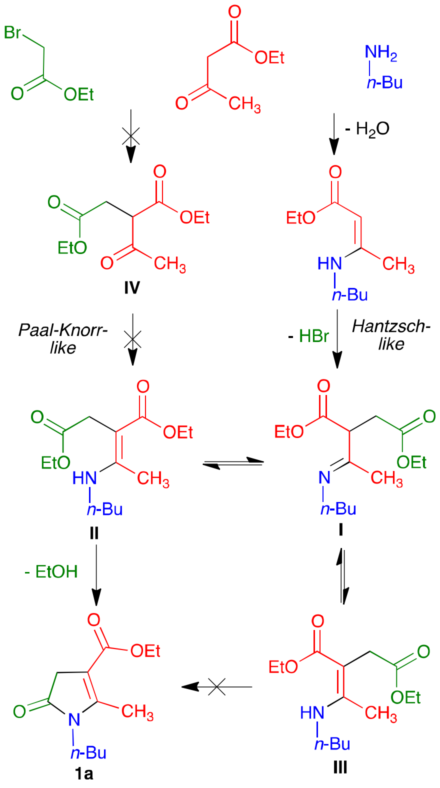
Table 2. Results of the synthesis of compounds **1**[a]

Entry	Cmpd	R^1	R^2	R^3	R^4	Yield (%)
1	**1a**	*n*-Bu	Me	OEt	H	60
2	**1b**	*n*-Bu	Me	OMe	H	50
3	**1c**	*n*-Bu	Me	Me	H	42
4	**1d**	*n*-Bu	*n*-Pr	OEt	H	52
5	**1e**	Bn	Me	OEt	H	52
6	**1f**	Bn	Me	OMe	H	55
7	**1g**	*n*-Bu	Et	OEt	H	59
8	**1h**	Me	Me	OEt	H	76
9	**1i**	*n*-Hex	*n*-Pr	OEt	H	72
10	**1j**	Allyl	Me	OMe	H	50
11	**1k**	2-Hydroxyethyl	Me	OMe	H	43
12	**1l**		Me	OMe	H	52
13	**1m**	*n*-Bu	Me	OEt	Ph	58[b]
14	**1n**	H	Me	OEt	H	55[c]
15	**1o**	H	Me	OEt	Me	43[c]
16	**1p**	H	Me	OEt	Et	40[c]
17	**1q**	H	Me	OEt	Ph	41[c]

[a] The X leaving group was Br in all cases except for entry 13, where X = I. [b] In this case the catalyst was aluminium trichloride (10%). [c] From ethyl β-aminocrotonate and the suitable α-bromoester.

Mechanistically, our three-component process was expected to proceed *via* a Hantzsch-type mechanism that is depicted in Scheme 4 for the reaction leading to compound **1a**. Thus, the reaction would start with the $InCl_3$-catalyzed formation of a β-enamino ester[20], which would then react with the α-haloester to give intermediate **I**, which can tautomerize to species **II** or **III**. However, only the *E* isomer **II** can undergo cyclization, thus driving these equilibria to the final product.

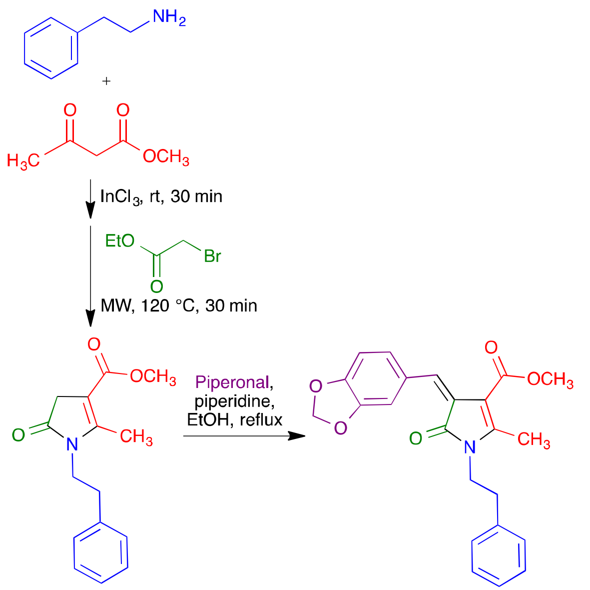
An alternative Paal-Knorr-like mechanism would involve the formation of a 1,4-dicarbonyl species **IV** that would then react with the primary amine to give the previous intermediate **II**. However, we verified that ethyl acetoacetate and ethyl bromoacetate did not react at all in the presence of $InCl_3$



Scheme 4. Mechanistic proposal for the three-component 2-pyrrolin-5-one synthesis

under our conditions. Furthermore, we found that treatment of the known[21] ethyl acetosuccinate **IV** with *n*-butylamine failed to give the 2-pyrrolin-5-one **1a** under our conditions. Onthe contrary, the isolated β-enamino ester arising from *n*-butylamine and ethyl acetoacetate[22] furnished compound **1a** when treated with ethyl bromoacetate in the presence of $InCl_3$ under our usual conditions.

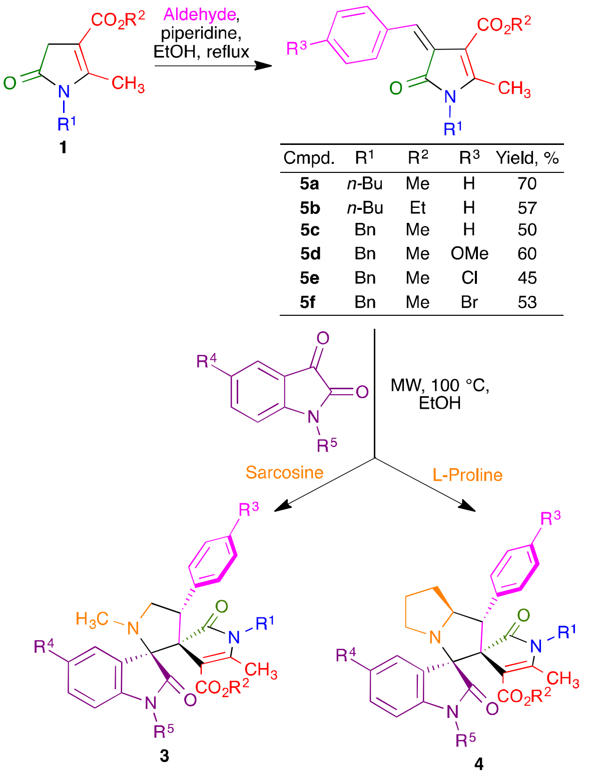
We next turned our attention to the application of the method to a target-oriented synthesis project. To this end, as mentioned in the Introduction, we chose as our target a 2-pyrrolin-5-one derivative (compound **2**) that had been previously proposed as an inhibitor of HIV integrase on the basis of thorough computational studies,[11] but which has never been studied experimentally owing to the lack of suitable synthetic access. Our synthesis of **2** is shown in Scheme 5, and comprised the preparation of pyrrolinone **1r** from β-phenetylamine, methyl acetoacetate and ethyl bromoacetate under our standard conditions, followed by its Knoevenagel condensation with piperonal.[23]



1r (54%) **2** (60%)

Scheme 5. Synthesis of compound **2**, a HIV integrase inhibition candidate proposed by computational methods

Finally, we examined the construction of a library of complex spirocyclic systems by combining our Hantzsch-like process with a second multicomponent reaction having as the key step the [3+2] dipolar cycloaddition between non-stabilized azomethine ylides, prepared *in situ* from isatin and α-amino acids, with activated olefins prepared by Knoevenagel reactions of our 2-pyrrolin-5-ones **1** with aromatic aldehydes.[24] Compounds **5** thus obtained were then used as dipolarophiles for the construction of the spiropyrrolidine library. Starting from five isatine derivatives and two N-substituted amino acids, the target dispiro compounds were obtained generally in good yields under focused microwave irradiation at 100 °C in ethanol solution (Scheme 6 and Table 3). Probably because of



Cmpd.	R¹	R²	R³	Yield, %
5a	*n*-Bu	Me	H	70
5b	*n*-Bu	Et	H	57
5c	Bn	Me	H	50
5d	Bn	Me	OMe	60
5e	Bn	Me	Cl	45
5f	Bn	Me	Br	53

Scheme 6. Regio- and diastereoselective synthesis of 2-pyrrolin-5-one-derived dispiro compounds via a three-component reaction having a 1,3-dipolar cycloaddition as the key step

Table 3. Results obtained in the synthesis of dispiro compounds **3** and **4**

Entry	Cmpd	R^1	R^2	R^3	R^4	R^5	Yield (%)
1	**3a**	*n*-Bu	Me	H	H	H	50
2	**3b**	*n*-Bu	Me	H	Cl	H	56
3	**3c**	Bn	Me	H	Cl	H	73
4	**3d**	Bn	Me	H	I	H	52
5	**3e**	Bn	Me	H	Me	H	55
6	**3f**	Bn	Me	H	H	H	65
7	**3g**	Bn	Me	H	H	Bn	75
8	**3h**	Bn	Me	OMe	H	Bn	68
9	**3i**	Bn	Me	OMe	H	H	55
10	**3j**	Bn	Me	OMe	Cl	H	73
11	**3k**	Bn	Me	OMe	I	H	50
12	**3l**	Bn	Me	OMe	Me	H	54
13	**3m**	Bn	Me	Cl	H	H	78
14	**3n**	Bn	Me	Br	H	H	88
15	**4a**	*n*-Bu	Me	H	H	H	42
16	**4b**	*n*-Bu	Et	H	H	H	38

steric hindrance, our protocol was more efficient in the case of reactions starting from sarcosine as the amino acid component in comparison with those involving the use of proline.

The compounds thus obtained were fully characterized by NMR studies. Thus, a NOESY experiment carried out on compound **4b** shows NOE enhancements between the phenyl *o*-proton and the α-amino proton, suggesting the *endo* structure **I** (see Scheme 6 below). Furthermore, the benzylic proton gives a NOE with one of the CH_2 hydrogens, which is compatible only with structure **I**, since in the alternative *exo* structure **II** the benzyl hydrogen and the CH_2 are too far away to provide a NOE. The proposed structure was finally confirmed by a single-crystal X-Ray diffraction study of compound **4b** (Figure 1).[25]

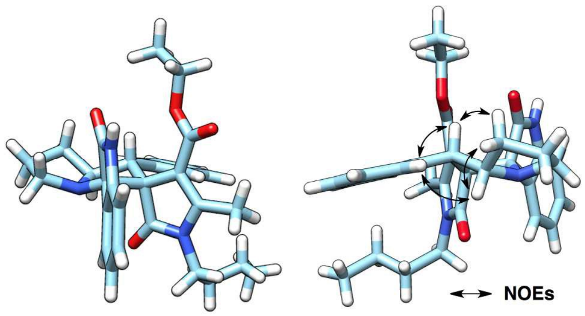
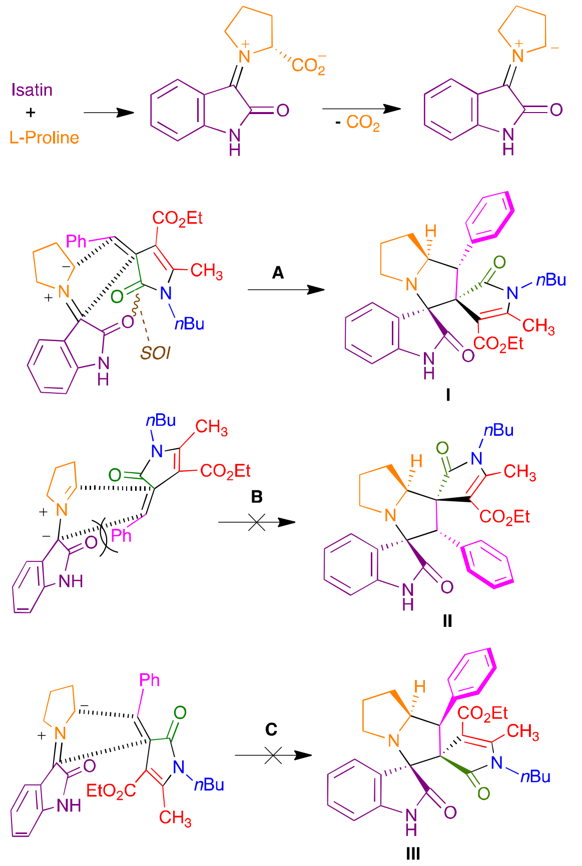


Figure 1. Single-crystal X-Ray diffraction study of compound **4b**, including a summary of the NOE effects observed in the NOESY experiment.

A mechanism that explains the regio- and diastereoselective isolation of compounds **3** and **4** is given in Scheme 7, using the case of **4b** as a representative example. Condensation of proline with isatin followed by decarboxylation[26] furnishes a nitrogen ylide, which acts as the 1,3-dipole in the reaction. This intermediate could in principle react with the dipolarophile following the alternative pathways **A** and **B**, which would afford two different regioisomers **I** and **II**, respectively. However, only product **I**, formed through path **A**, was observed, which can be explained by the steric clash between the phenyl and carbonyl groups of both reacting species in pathway **B**. The preference for the structure *endo* **I** over the *exo* **III**, arising through pathway **C**, can be attributed to a favourable secondary orbital interaction (SOI) effect between the carbonyl groups of the dipolarophile and the dipole in the transition state corresponding to pathway **A**.[27]



Scheme 7. Mechanistic proposal accounting for the regio- and diastereoselectivity of the three-component reaction leading to dispiro compounds **3** and **4**

Experimental Section

General experimental details.

All reagents and solvents were of commercial quality and were used as received. Reactions were monitored by thin layer chromatography on aluminium plates coated with silica gel and fluorescent indicator. Microwave-assisted reactions were performed on a CEM Discover focused microwave reactor. Separations by flash chromatography were performed using a Combiflash Teledyne automated flash chromatograph or on conventional silica gel columns. Melting points were measured with a Kofler-type heating platine microscope from Reichert, 723 model, and are uncorrected. Infrared spectra were recorded with an Agilent Cary630 FTIR spectrophotometer with a diamond ATR accessory for solid and liquid samples, requiring no sample preparation; wavenumbers are given in cm^{-1}. NMR spectroscopic data were obtained using spectrometers maintained by the CAI de Resonancia Magnética, UCM, operating at 250 MHz for ^1H NMR and 63 MHz for ^{13}C NMR; chemical shifts are given in (δ) parts per million and coupling constants (*J*) in hertz. Elemental analyses were determined by the CAI de Microanálisis, Universidad Complutense, using a Leco CHNS-932 combustion microanalyzer.

General procedure for the synthesis of 2-pyrrolin-5-one derivatives 1

To a suspension of indium trichloride (5% mmol) in the corresponding β-dicarbonyl compound (1 eq), placed in a microwave reaction vial, was added the suitable amine (1-1.2 eq). The mixture was stirred at room temperature for 30 minutes and monitored by TLC. After the reaction completion, the excess of amine was evaporated under reduced pressure.

Then, the non-isolated enamino ester and the appropriate α-haloester (1 eq) were exposed to focused microwave irradiation at 120 °C for 30 minutes. Once the reaction was completed, the mixture was diluted with $CHCl_3$ (20 mL) and washed with water (2 x 5 mL). The organic phase was dried over anhydrous sodium sulphate and then evaporated under reduced pressure. The mixture was cromatographed on silica gel using as eluent a mixture of hexane/ethyl acetate.

Ethyl 1-butyl-2-methyl-5-oxo-4,5-dihydro-1*H*-pyrrole-3-carboxylate (1a). Orange solid (135 mg, 60%): mp 62-68 °C; ^{1}H-NMR (250 MHz, $CDCl_3$): δ 4.21 (q, *J* = 7.2 Hz, 2H), 3.55-3.49 (m, 2H), 3.27 (q, *J* = 2.4 Hz, 2H), 2.47 (t, *J* = 2.4 Hz, 3H), 1.61-1.49 (m, 2H), 1.43-1.24 (m, 2H), 1.31 (t, *J* = 7.2 Hz, 3H), 0.96 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (63 MHz, $CDCl_3$): δ 176.4, 163.9, 159.8, 103.3, 59.6, 37.0, 36.6, 31.5, 20.1, 14.4, 13.7, 12.9; IR (neat, cm^{-1}): 1725, 1691, 1226. Anal. calcd. for $C_{12}H_{19}NO_3$: C 63.98, H 8.50, N 6.22%. Found: C 63.66, H 8.33, N 5.97%.

Methyl 1-butyl-2-methyl-5-oxo-4,5-dihydro-1*H*-pyrrole-3-carboxylate (1b). Yellow oil (111 mg, 50%); ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.72 (s, 3H), 3.50 (t, *J* = 7.2 Hz, 2H), 3.24 (q, *J* = 2.3 Hz, 2H), 2.44 (t, *J* = 2.3 Hz, 3H), 1.59-1.45 (m, 2H), 1.43-1.23 (m, 2H), 0.93 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 176.4, 165.1, 155.0, 103.4, 51.4, 40.4, 37.0, 31.8, 20.5, 14.1, 12.7; IR (neat, cm^{-1}): 1723, 1690, 1223. Anal. calcd. for $C_{11}H_{17}NO_3$: C 62.54, H 8.11, N 6.63%. Found: C 62.43, H 7.89, N 6.19%.

4-Acetyl-1-butyl-5-methyl-1,3-dihydro-2*H*-pyrrole-2-one (1c). Yellow oil (82 mg, 42%); ^{1}H-NMR (250 MHz, $CDCl_3$): δ 3.57-3.51 (m, 2H), 3.34 (q, *J* = 2.3 Hz, 2H), 2.50 (t, *J* = 2.3 Hz, 3H), 2.22 (s, 3H), 1.58 -1.49 (m, 2H), 1.44-1.29 (m, 2H), 0.96 (t, *J* = 7.0 Hz, 3H); ^{13}C-NMR (63 MHz, $CDCl_3$): δ 192.8, 175.4, 154.0, 111.8, 39.8, 37.1, 31.2, 29.5, 20.0, 13.6, 12.8; IR (neat, cm^{-1}): 1721, 1659. Anal. calcd. for $C_{11}H_{17}NO_2$: C 67.66, H 8.78, N 7.17%. Found: C 67.32, H 8.44, N 6.81%.

Ethyl 1-butyl-5-oxo-2-propyl-4,5-dihydro-1*H*-pyrrole-3-carboxylate (1d). Orange oil (132 mg, 52%); ^{1}H-NMR: (250 MHz, $CDCl_3$): δ 4.18 (q, *J* = 7.1 H, 2H), 3.50-3.44 (m, 2H), 3.24 (s, 2H), 2.82-2.76 (m, 2H), 1.64-1.48 (m, 4H), 1.40-1.23 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.03 (t, *J* = 7.3 Hz, 3H), 0.93 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR: (63 MHz, $CDCl_3$): δ 176.3, 163.9, 158.3, 102.9, 59.6, 40.0, 36.6, 31.3, 27.6, 22.0, 20.0, 14.3, 14.0, 13.6; IR (neat, cm^{-1}): 1728, 1694, 1218. Anal. calcd. for $C_{14}H_{23}NO_3$: C 66.37, H 9.15, N 5.53%. Found: C 65.33, H 9.00, N 5.36%.

Ethyl 1-benzyl-2-methyl-5-oxo-4,5-dihydro-1*H*-pyrrole-3-carboxylate (1e). Yellow oil (135 mg, 52%); ^{1}H-NMR: (250 MHz, $CDCl_3$): δ 7.39-7.30 (m, 3H), 7.22 (dd, *J* = 8.0 Hz, *J* = 1.8 Hz, 2H), 4.79 (s, 2H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.41 (q, *J* = 2.4 Hz, 2H), 2.37 (t, *J* = 2.4 Hz, 3H), 1.32 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR: (63 MHz, $CDCl_3$): δ 176.0, 164.2, 154.0, 136.5, 128.9, 127.7, 126.8, 103.7, 59.8, 43.4, 36.6, 14.4, 12.6; IR (neat, cm^{-1}): 1726, 1693, 1227. Anal. calcd. for $C_{15}H_{17}NO_3$: C 69.48, H 6.61, N 5.40%. Found: C 69.16, H 6.89, N 5.31%.

Methyl 1-benzyl-2-methyl-5-oxo-4,5-dihydro-1*H*-pyrrole-3-carboxylate (1f). Pale brown solid (135 mg, 55%): mp 82-84 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.42-7.15 (m, 5H), 4.79 (s, 2H), 3.75 (s, 3H), 3.40 (q, *J* = 2.4 Hz, 2H), 2.37 (t, *J* = 2.4 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 176.4, 154.8, 136.9, 129.3, 128.2, 127.3, 103.8, 51.5, 43.9, 37.0, 13.0; IR (neat, cm^{-1}): 1727, 1685, 1250. Anal. calcd. for $C_{14}H_{15}NO_3$: C 68.56, H 6.16, N 5.71%. Found: C 68.53, H 6.08, N 5.78%.

Ethyl 1-butyl-2-ethyl-5-oxo-4,5-dihydro-1*H*-pyrrole-3-carboxylate (1g). Yellow oil (142 mg, 59%); ^{1}H-NMR: (250 MHz, $CDCl_3$): δ 4.22 (q, *J* = 7.1 Hz, 2H), 3.55-3.48 (m, 2H), 3.27 (s, 2H), 2.90-2.83 (m, 2H), 1.65-1.40 (m, 4H), 1.39-1.23 (m, 6H), 0.93 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR: (63 MHz, $CDCl_3$): δ 176.4, 163.9, 159.8, 102.9, 59.6, 40.0, 36.6, 31.5, 20.1, 19.2, 14.4, 13.7, 12.9; IR (neat, cm^{-1}): 1726, 1693, 1228. Anal. calcd. for $C_{13}H_{21}NO_3$: C 65.25, H 8.84, N 5.85%. Found: C 65.16, H 8.89, N 5.79%.

Ethyl 1,2-dimethyl-5-oxo-4,5-dihydro-1*H*-pyrrole-3-carboxylate (1h). Yellow oil (140 mg, 76%); ^{1}H-NMR: (250 MHz, $CDCl_3$): δ 4.17 (q, *J* = 7.1 Hz, 2H), 3.05 (s, 3H), 3.23 (q, *J* = 2.4 Hz, 2H), 2.42 (t, *J* = 7.1 Hz, 3H), 1.27 (t, 3H, *J* = 2.4 Hz); ^{13}C-NMR: (63 MHz, $CDCl_3$): δ 176.0, 164.2, 154.1, 103.2, 59.7, 36.5, 26.3, 14.3, 12.4; IR (neat, cm^{-1}): 1725, 1692, 1228. Anal. calcd. for $C_9H_{13}NO_3$: C 59.00, H 7.15, N 7.65%. Found: C 59.22, H 7.30, N 7.52%.

Ethyl 1-hexyl-5-oxo-2-propyl-4,5-dihydro-1*H*-pyrrole-3-carboxylate (1i). Orange oil (203 mg, 72%); ^{1}H-NMR: (250 MHz, $CDCl_3$): δ 4.20 (q, *J* = 7.1 Hz, 2H), 3.57-3.48 (m, 2H), 3.27 (s,2H), 2.82-2.76 (m, 2H), 1.63-1.57 (m, 4H), 1.34-1.26 (m, 6H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.05 (t, *J* = 7.5 Hz, 3H), 0.91 (t, *J* = 7.0 Hz, 3H); ^{13}C-NMR: (63 MHz, $CDCl_3$): δ 176.4, 163.9, 158.3, 102.9, 59.6, 40.3, 36.6, 31.3, 29.3, 27.7, 26.5, 22.5, 22.0, 14.4, 14.1, 14.0; IR (neat, cm^{-1}): 1726, 1702, 1227. Anal. calcd. for $C_{16}H_{27}NO_3$: C 68.29, H 9.67, N 4.98%. Found: C 68.22, H 9.30, N 4.82%.

Methyl 1-allyl-2-methyl-5-oxo-4,5-dihydro-1*H*-pyrrole-3-carboxylate (1j). Yellow oil (98 mg, 50%); ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.84-5.62 (m, 1H), 5.16-4.96 (m, 2H), 4.11 (dt, *J* = 5.0, 1.7 Hz, 2H), 3.67 (s, 3H), 3.24 (q, *J* = 2.4 Hz, 2H), 2.36 (t, *J* = 2.4 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 174.6, 163.6, 153.5, 131.3, 115.8, 102.1, 50.1, 41.0, 35.5, 11.2; IR (neat, cm^{-1}): 1720, 1685, 1228. Anal. calcd. for $C_{10}H_{13}NO_3$ C 61.53, H 6.71, N 7.18%. Found: C 61.19, H 6.65, N 6.98%.

Methyl 1-(2-hydroxyethyl)-2-methyl-5-oxo-4,5-dihydro-1*H*-pyrrole-3-carboxylate (1k). Pale red solid (86 mg, 43%): mp 111-114 °C; NMR data are identical to those found in the literature.[9] IR (neat, cm^{-1}): 3482, 2940, 1715, 1669, 1616, 1231. Anal. calcd. for $C_9H_{13}NO$: C 54.26, H, 6.58, N, 7.03%. Found: C 54.14, H 6.39, N 6.79%.

Methyl 1-(3,4-dimethoxyphenethyl)-2-methyl-5-oxo-4,5-dihydro-1*H*-pyrrole-3-carboxylate (1l). Beige solid (166 mg, 52%): mp 99-103 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.73 (d, *J* = 8.0 Hz, 1H), 6.65 (d, *J* = 1.9 Hz, 1H), 6.60-6.59 (m, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.68-3.59 (m, 5H), 3.19 (q, *J* = 2.3 Hz, 2H), 2.75 (t, *J* = 7.3 Hz, 2H), 2.13 (t, *J* = 2.4 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 175.0, 163.6, 153.5, 148.0, 146.9, 129.4, 119.8, 110.9, 110.3, 101.8, 88.8, 54.9, 50.0, 41.1, 35.5, 33.7, 11.0. IR (neat, cm^{-1}): 1717, 1685, 1220. Anal. calcd. for $C_{17}H_{21}NO_5$: C 63.94, H 6.63, N 4.39%. Found: C 63.77, H 6.47, N 4.29%.

Ethyl 1-butyl-2-methyl-5-oxo-4-phenyl-4,5-dihydro-1*H*-pyrrole-3-carboxylate (1m). Orange oil (175 mg, 58%); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.35-7.15 (m, 5H), 4.36 (q, *J* = 2.0 Hz, 1H), 4.13-3.97 (m, 2H), 3.58 (m, 2H), 2.48 (d, *J* = 2.0 Hz, 3H), 1.65-1.53 (m, 2H), 1.41-1.28 (m, 2H), 1.06 (t, *J* = 7.2 Hz, 3H), 0.95 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (63 MHz, CDCl$_3$): δ 177.8, 164.5, 155.0, 137.0, 129.0, 128.3, 127.6, 108.9, 60.0, 53.2, 40.4, 31.8, 20.4, 14.5, 14.1, 12.7. IR (neat, cm^{-1}): 1721, 1696, 1218. Anal. calcd. for $C_{18}H_{23}NO_3$: C 71.73, H 7.69, N, 4.65%. Found: C 71.65, H 7.64, N 4.69%.

Ethyl 2-methyl-5-oxo-4,5-dihydro-1*H*-pyrrole-3-carboxylate (1n). Beige solid (93 mg, 55%): mp 119-123 °C; ^{1}H NMR (250 MHz, CDCl$_3$): δ 8.72 (br s, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.32 (q, *J* = 2.3 Hz, 2H), 2.39 (t, *J* = 2.3 Hz, 3H), 1.32 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (63 MHz, CDCl$_3$): δ 178.7, 164.6, 152.0, 104.9, 60.3, 38.0, 14.8, 13.9; IR (neat, cm^{-1}): 3165, 1702, 1682, 1251. Anal. calcd. for $C_8H_{11}NO_3$: C 56.80, H 6.55, N 8.28%. Found: C 56.42, H 6.36, N 7.90%.

Ethyl 2,4-dimethyl-5-oxo-4,5-dihydro-1*H*-pyrrole-3-carboxylate (1o). Yellow oil (79 mg, 43%); ^{1}H NMR (250 MHz, CDCl$_3$): δ 8.11 (br s, 1H), 4.42-4.09 (m, 2H), 3.29 (qq, *J* = 7.6, 2.1 Hz, 1H), 2.40 (d, *J* = 2.1 Hz, 3H), 1.44 (d, *J* = 7.6 Hz, 3H), 1.33 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (63 MHz, CDCl$_3$): δ 182.1, 164.7, 150.9, 110.7, 60.1, 43.5, 15.6, 14.8, 14.0; IR (neat, cm^{-1}): 1723.1, 1690.4, 1223.0; IR (neat, cm^{-1}): 3186, 1721, 1686, 1249. Anal. calcd. for $C_9H_{13}NO_3$: C 59.00, H 7.15, N 7.65%. Found: C 58.79, H 6.95, N 7.73%.

Ethyl 4-ethyl-2-methyl-5-oxo-4,5-dihydro-1*H*-pyrrole-3-carboxylate (1p). Yellow oil (79 mg, 40%); ^{1}H NMR (250 MHz, CDCl$_3$): δ 8.22 (br s, 1H), 4.34-4.14 (m, 2H), 3.43-3.29 (m, 1H), 2.41 (d, *J* = 2.2 Hz, 3H), 2.18-1.88 (m, 2H), 1.33 (t, *J* = 7.1 Hz, 3H), 0.83 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (63 MHz, CDCl$_3$): δ 181.5, 164.7, 151.8, 108.1, 60.1, 48.9, 22.7, 14.8, 14.1, 9.4; IR (neat, cm^{-1}): 3257, 1715, 1689, 1223. Anal. calcd. for $C_{10}H_{15}NO_3$: C 60.90, H 7.67, N 7.10%. Found: C 60.88, H 7.48, N 7.13%.

Ethyl 2-methyl-5-oxo-4-phenyl-4,5-dihydro-1*H*-pyrrole-3-carboxylate (1q) Yellow oil (101 mg, 41%); ^{1}H NMR (250 MHz, CDCl$_3$): δ 8.21 (br s, 1H), 7.44-7.15 (m, 5H), 4.42 (app. d, *J* = 2.2 Hz, 1H), 4.18-3.93 (m, 2H), 2.47 (d, *J* = 2.2 Hz, 3H), 1.09 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (63 MHz, CDCl$_3$): δ 179.4, 164.3, 152.9, 136.4, 129.1, 128.3, 127.9, 109.8, 60.1, 54.2, 14.5, 14.0; IR (neat, cm^{-1}): 3238, 1719, 1687, 1223. Anal. calcd. for $C_{14}H_{15}NO_3$: C 68.56, H 6.16, N 5.71%. Found: C 68.41, H 6.16, N 5.57%.

Methyl 2-methyl-5-oxo-1-phenethyl-4,5-dihydro-1*H*-pyrrole-3-carboxylate (1r). Light brown solid (140 mg, 54%): mp 99-103 °C; ^{1}H NMR (250 MHz, CDCl$_3$): δ 7.20-6.91 (m, 5H), 3.56 (t, *J* = 7.3 Hz, 2H), 3.53 (s, 3H), 3.08 (q, *J* = 2.2 Hz, 2H), 2.69 (t, *J* = 7.3 Hz, 2H), 2.00 (t, *J* = 2.2 Hz, 3H); ^{13}C NMR (63 MHz, CDCl$_3$): δ 175.0, 163.6, 153.5, 137.0, 127.8, 127.7, 125.9, 101.9, 50.0, 41.0, 35.5, 34.2, 11.0; IR (neat, cm^{-1}): 1703, 1669, 1230. Anal. calcd. for $C_{15}H_{17}NO_3$: C 69.48, H 6.61, N 5.40%. Found: C 69.19, H 6.50, N 5.15%.

General procedure for the synthesis of 4-arylmethylen-2-pyrrolin-5-ones (compound 2 and compounds 5)

In a round-bottomed flask, the suitable 2-pyrrolin-5-one (1 eq) was suspended in ethanol (10 mL). Then, the corresponding aldehyde (1.1 eq) and piperidine (2 eq) were added. The mixture was refluxed for 1 h and monitored by TLC. Once the reaction was completed the mixture was cooled to room temperature, diluted with ethyl acetate (20 mL) and washed with water (2 x 10 mL) The organic phase was dried over anhydrous sodium sulphate and then evaporated under reduced pressure. The mixture was cromatographed on silica gel using as eluent a mixture of hexane/ethyl acetate.

Methyl (*Z*)-4-(benzo[*d*][1,3]dioxol-5-ylmethylene)-2-methyl-5-oxo-1-phenethyl-4,5-dihydro-1*H*-pyrrole-3-carboxylate (2). Yellow solid (235 mg, 60%): mp 179 °C; ^{1}H NMR (250 MHz, CDCl$_3$): δ 8.17 (d, *J* = 1.6Hz, 1H), 8.13 (s, 1H), 7.56 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.38-7.11 (m, 5H), 6.88 (d, *J* = 8.2 Hz, 1H), 6.05 (s, 2H), 3.87 (t, *J* = 7.3 Hz, 2H), 3.85 (s, 3H), 2.93 (t, *J* = 7.3 Hz, 2H,), 2.25 (s, 3H); ^{13}C NMR (63 MHz, CDCl$_3$) δ 166.1, 165.3, 151.9, 149.9, 147.8, 141.9, 138.6, 129.6, 129.3, 129.1, 127.2, 125.1, 111.7, 108.3, 103.9, 101.9, 51.3, 42.5, 35.8, 13.4. IR (neat, cm^{-1}): 1672, 1264. Anal. calcd. for $C_{23}H_{11}NO_5$: C 70.58, H 5.41, N 3.58%. Found: C 70.38, H 5.32, N 3.67%.

Methyl (*Z*)-4-benzylidene-1-butyl-2-methyl-5-oxo-4,5-dihydro-1*H*-pyrrole-3-carboxylate (5a). Yellow solid (210 mg, 70%): mp 84-87 °C; ^{1}H NMR (250 MHz, CDCl$_3$): δ 8.14 (s, 1H), 8.11-7.99 (m, 2H), 7.45-7.30 (m, 3H), 3.84 (s, 3H), 3.68-3.52 (m, 2H), 2.53 (d, *J* = 0.5 Hz, 3H), 1.67-1.47 (m, 2H), 1.44-1.22 (m, 2H), 0.93 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (63 MHz, CDCl$_3$): δ 166.1, 165.3, 155.9, 153.5, 141.6, 135.1, 131.9, 130.3, 128.3, 127.1, 51.3, 40.4, 31.9, 20.6, 14.2, 13.8; IR (neat, cm^{-1}): 1699, 1689, 1601, 1213. Anal. calcd. for $C_{18}H_{21}NO_3$: C 72.22, H 7.07, N 4.68%. Found: C 72.17, H 6.94, N 4.59%.

Ethyl (*Z*)-4-benzylidene-1-butyl-2-methyl-5-oxo-4,5-dihydro-1*H*-pyrrole-3-carboxylate (5b). Yellow solid (179 mg, 57%): mp 161-163 °C; ^{1}H NMR (250 MHz, CDCl$_3$): δ 8.20 (s, 1H), 7.41 (dd, *J* = 4.8, 2.5 Hz, 2H), 7.43-7.29 (m, 3H), 4.35 (q, *J* = 7.1 Hz, 2H), 3.64 (t, *J* = 7.6 Hz, 2H), 2.56 (s, 3H), 1.66-1.51 (m, 2H), 1.42 (t, *J* = 7.1 Hz, 3H), 1.42-1.30 (m, 2H), 0.96 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (63 MHz, CDCl$_3$): δ 166.2, 164.8, 153.3, 141.6, 135.1, 131.9, 130.3, 128.4, 127.2, 103.9, 60.2, 40.3, 31.9, 20.6, 14.9, 14.2, 13.8; IR (neat, cm^{-1}): 1672, 1158. Anal. calcd. for $C_{19}H_{23}NO_3$: C 72.82, H 7.40, N 4.47%. Found: C 72.85, H 7.34, N 4.51%.

Methyl (*Z*)-1-benzyl-4-benzylidene-2-methyl-5-oxo-4,5-dihydro-1*H*-pyrrole-3-carboxylate (5c). Yellow solid (167 mg, 50%): mp 83-86 °C; ^{1}H NMR (250 MHz, CDCl$_3$): δ 8.28 (s, 1H), 8.22-8.11 (m, 2H), 7.54-7.14 (m, 8H), 4.90 (s, 2H), 3.87 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (63 MHz, CDCl$_3$): δ 166.2, 165.2, 153.4, 142.2, 137.1, 135.0, 132.1, 130.5, 129.3, 128.4, 128.0, 127.2, 126.8, 104.3, 51.4, 43.8, 14.2; IR (neat, cm^{-1}): 1684, 1599, 1193. Anal. calcd. for $C_{21}H_{19}NO_3$: C 75.66, H 5.74, N 4.20%. Found: C 75.55, H 5.68, N 4.18%.

Methyl (*Z*)-1-benzyl-4-(4-methoxybenzylidene)-2-methyl-5-oxo-4,5-dihydro-1*H*-pyrrole-3-carboxylate (5d). Yellow solid (218 mg, 60%): mp 121-124 °C; ^{1}H NMR (250 MHz, CDCl$_3$): δ 8.39-8.08 (m, 3H), 7.47-7.10 (m, 5H), 7.03-6.83 (m, 2H), 4.93 (s, 2H), 3.89 (s, 3H), 3.86 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (63 MHz, CDCl$_3$): δ 164.2, 163.2, 159.6, 149.4, 140.2, 135.1, 132.6, 130.5, 127.1, 125.8, 125.0, 122.4, 111.8, 102.3, 53.6, 49.2, 41.6, 12.0; IR (neat, cm^{-1}): 1679.0, 1589.4, 1254.4. Anal. calcd. for $C_{22}H_{21}NO_4$: C 72.71, H 5.82, N 3.85%. Found: C 72.46, H 5.84, N 3.92%.

Methyl (*Z*)-1-benzyl-4-(4-chlorobenzylidene)-2-methyl-5-oxo-4,5-dihydro-1*H*-pyrrole-3-carboxylate (5e). Yellow solid (166 mg, 45%): mp 97-100 °C; ^{1}H NMR (250 MHz, CDCl$_3$): δ 8.09 (s, 1H), 8.00 (d, *J* = 8.4 Hz, 2H), 7.35-7.20 (m, 5H), 7.16-7.06 (m, 2H), 4.81 (s, 2H), 3.76 (s, 3H), 2.36 (d, *J* = 0.6 Hz, 3H); ^{13}C NMR (63 MHz, CDCl$_3$): δ 166.2, 165.1, 153.6, 140.6, 136.9, 136.3, 133.4, 129.4, 129.3, 128.7, 128.1, 127.3, 127.1, 104.2, 51.4, 43.8, 14.2; IR (neat, cm^{-1}): 1691, 1677, 1602, 1196. Anal. calcd. for $C_{21}H_{18}ClNO_3$: C 68.57, H 4.93, N 3.81%. Found: C 68.20, H 4.88, N 3.81%.

Methyl (*Z*)-1-benzyl-4-(4-bromobenzylidene)-2-methyl-5-oxo-4,5-dihydro-1*H*-pyrrole-3-carboxylate (5f). Yellow solid (219 mg, 53%): mp 136 °C; ^{1}H NMR (250 MHz, CDCl$_3$): δ 8.16 (s, 1H), 8.02 (d, *J* = 8.5 Hz, 2H), 7.55 (d, *J* = 8.5, 2H), 7.48-7.14 (m, 5H), 4.90 (s, 2H), 3.86 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (63 MHz, CDCl$_3$): δ 166.2, 165.1, 153.7, 140.6, 136.9, 133.8, 133.6, 131.6, 129.3, 128.1, 127.3, 127.2, 124.9, 104.2, 51.4, 43.8, 14.2; IR (neat, cm^{-1}): 1691.8, 1674.4, 1602.0, 1196.6; IR (neat, cm^{-1}): 3190, 1708, 1681, 1612, 1249, 1203. Anal. calcd. for $C_{21}H_{18}BrNO_3$: C 61.18, H 4.40, N 3.40%. Found: C 60.99, H 4.38, N 3.26%.

General procedure for the synthesis of dispirooxindoles 3 and 4

The suitable isatine (1.5 eq.) and the appropriate aminoacid (1.5 eq) were placed in a microwave reaction vial. Then the corresponding 4-arylmethylen-2-pyrrolin-5-one (1 eq) suspended in ethanol (2 mL) was added and irradiated at 100 °C for 1h. After the reaction completion, the mixture was cooled at room temperature and a precipitate was formed. The solid compound was filtered and washed twice with cold ethanol. No further purification was needed.

Methyl (3*S,3'*R**,4'*R**)-1''-butyl-1',5''-dimethyl-2,2''-dioxo-4'-phenyl-1'',2''-dihydrodispiro[indoline-3,2'-pyrrolidine-3',3''-pyrrole]-4''-carboxylate (3a).** Pale brown solid (237 mg, 50%): mp 215-218 °C; ^{1}H NMR (250 MHz, CDCl$_3$): δ 7.90 (br s, 1H), 7.44-7.29 (m, 2H), 7.29-7.03 (m, 5H), 6.86 (td, *J* = 7.7, 0.9 Hz, 1H), 6.74 (d, *J* = 7.7 Hz, 1H), 5.34 (dd, *J* = 10.1, 8.7 Hz, 1H), 4.24 (t, *J* = 8.7 Hz, 1H), 3.78 (s, 3H), 3.65 (dd, *J* = 10.1, 8.7 Hz, 1H), 3.34-3.13 (m, 1H), 3.02-2.78 (m, 1H), 2.34 (s, 3H), 1.96 (s, 3H), 1.17-0.94 (m, 2H), 0.94-0.79 (m, 2H), 0.79-0.62 (m, 3H); ^{13}C NMR (63 MHz, CDCl$_3$): δ 178.1, 175.2, 165.6, 156.0, 142.5, 137.7, 129.7, 129.3, 128.3, 127.1, 126.0, 122.4, 110.2, 103.6, 78.2, 68.2, 56.2, 51.2, 43.5, 39.7, 36.3, 30.9, 20.0, 14.1, 12.8; IR (neat, cm^{-1}): 3140, 1725, 1702, 1688, 1602, 1208. Anal. calcd. for $C_{28}H_{31}N_3O_4$: C 71.02, H 6.60, N 8.87%. Found: C 70.84, H 6.54, N 8.85%.

Methyl (3*S,3'*R**,4'*R**)-1''-butyl-5-chloro-1',5''-dimethyl-2,2''-dioxo-4'-phenyl-1'',2''-dihydrodispiro[indoline-3,2'-pyrrolidine-3',3''-pyrrole]-4''-carboxylate (3b).** Pale brown solid (284 mg, 56%): mp 102-104 °C; ^{1}H NMR (250 MHz, CDCl$_3$): δ 8.55 (br s, 1H), 7.35 (dd, *J* = 7.9, 1.4 Hz, 2H), 7.29-7.05 (m, 5H), 6.74 (d, *J* = 8.3 Hz, 1H), 5.34 (dd, *J* = 9.9, 8.7 Hz, 1H), 4.22 (t, *J* = 8.7 Hz, 1H), 3.73 (s, 3H), 3.69-3.56 (m, 1H), 3.23-2.98 (m, 2H), 2.34 (s, 3H), 1.99 (s, 3H), 1.29-1.07 (m, 1H), 1.07-0.83 (m, 3H), 0.78 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (63 MHz, CDCl$_3$): δ 179.5, 176.3, 166.8, 157.4, 142.5, 138.7, 131.0, 130.6, 129.6, 129.2, 129.2, 128.5, 127.7, 112.7, 104.6, 79.5, 69.6, 57.5, 52.5, 44.9, 41.2, 37.6, 32.4, 21.4, 15.3, 14.3; IR (neat, cm^{-1}): 3238, 1717, 1689, 1613, 1210, 1175. Anal. calcd. for $C_{28}H_{30}ClN_3O_4$: C 66.20, H 5.95, N 8.27%. Found: C 66.02, H 5.71, N 8.21%.

Methyl (3*S,3'*R**,4'*R**)-1''-benzyl-5-chloro-1',5''-dimethyl-2,2''-dioxo-4'-phenyl-1'',2''-dihydrodispiro[indoline-3,2'-pyrrolidine-3',3''-pyrrole]-4''-carboxylate (3c).** Beige solid (396 mg, 73%): mp 166-169 °C; ^{1}H NMR (250 MHz, CDCl$_3$): δ 8.06 (br s, 1H), 7.49-7.34 (m, 2H), 7.28-6.89 (m, 8H), 6.67 (d, *J* = 8.3 Hz, 1H), 6.23 (d, *J* = 7.0 Hz, 2H), 5.37 (dd, *J* = 10.0, 8.5 Hz, 1H), 4.81 (d, *J* = 16.3 Hz, 1H), 4.24 (t, *J* = 8.5 Hz, 1H), 3.88 (d, *J* = 16.3 Hz, 1H), 3.77-3.51 (m, 4H), 2.30 (s, 3H), 1.72 (s, 3H); ^{13}C NMR (63 MHz, CDCl$_3$): δ 177.7, 175.0, 165.4, 156.1, 141.0, 137.3, 136.1, 129.9, 129.6, 129.1, 128.6, 128.2, 127.9, 127.5, 127.4, 126.2, 111.3, 103.7, 78.4, 77.6, 68.8, 56.0, 51.3, 43.5, 43.0, 36.3, 13.2; IR (neat, cm^{-1}): 3224, 1721, 1692, 1617, 1255, 1181. Anal. calcd. for $C_{31}H_{28}ClN_3O_4$: C 68.69, H 5.21, N 7.75%. Found C 68.75, H 5.10, N 7.67%.

Methyl (3*S,3'*R**,4'*R**)-1''-benzyl-5-iodo-1',5''-dimethyl-2,2''-dioxo-4'-phenyl-1'',2''-dihydrodispiro[indoline-3,2'-pyrrolidine-3',3''-pyrrole]-4''-carboxylate (3d).** Beige solid (329 mg, 52%): mp 140-143 °C; ^{1}H NMR (250 MHz, CDCl$_3$): δ 7.70-7.61 (m, 2H), 7.55 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.52-7.43 (m, 2H), 7.36-7.27 (m, 3H), 7.19-7.00 (m, 3H), 6.61 (d, *J* = 8.2 Hz, 1H), 6.32 (d, *J* = 6.9 Hz, 2H), 5.44 (dd, *J* = 10.1, 8.5 Hz, 1H), 4.96 (d, *J* = 16.3 Hz, 1H), 4.34 (t, *J* = 8.5 Hz, 1H), 3.95 (d, *J* = 16.3 Hz, 1H), 3.80 (s, 3H), 3.72 (app. t, *J* = 9.6 Hz, 1H), 2.42 (s, 3H), 1.82 (s, 3H); ^{13}C NMR (63 MHz, CDCl$_3$): δ 175.0, 165.3, 156.3, 142.0, 138.7, 138.7, 136.1, 134.7, 129.6, 129.2, 128.7, 127.5, 127.4, 126.2, 112.3, 103.6, 85.1, 78.1, 77.6, 68.8, 56.1, 51.4, 43.4, 43.0, 36.5, 31.4, 13.2; IR (neat, cm^{-1}): 3222, 1719, 1688, 1607, 1177. Anal. calcd. for $C_{31}H_{28}IN_3O_4$: C 58.78, H 4.46, N 6.63%. Found C 58.67, H 4.39, N 6.71%.

Methyl (3*S,3'*R**,4'*R**)-1''-benzyl-1',5,5''-trimethyl-2,2''-dioxo-4'-phenyl-1'',2''-dihydrodispiro[indoline-3,2'-pyrrolidine-3',3''-pyrrole]-4''-carboxylate (3e).** Beige solid (287 mg, 55%): mp 217 °C; ^{1}H NMR (250 MHz, CDCl$_3$): δ 7.78 (br s, 1H), 7.61-7.42 (m, 2H), 7.31-7.29 (m, 3H), 7.20-6.93 (m, 5H), 6.70 (d, *J* = 7.8 Hz, 1H), 6.30 (d, *J* = 7.3 Hz, 2H), 5.48 (app. t, *J* = 8.9 Hz, 1H), 4.86 (d, *J* = 16.3 Hz, 1H), 4.33 (app. t, *J* = 8.9 Hz, 1H), 3.96 (d, *J* = 16.3 Hz, 1H), 3.81 (s, 3H), 3.72 (app. t, *J* = 9.6 Hz, 1H), 2.40 (s, 3H), 2.26 (s, 3H), 1.80 (s, 3H); ^{13}C NMR (63 MHz, CDCl$_3$): δ 177.9, 175.2, 165.5, 155.7, 140.0, 137.7, 136.3, 132.1, 130.1, 129.7, 129.1, 128.6, 127.5, 127.2, 126.5, 126.1, 126.0, 110.0, 104.1, 68.7, 56.1, 51.3, 43.5, 42.8, 36.4, 31.4, 21.5, 13.2; IR (neat, cm^{-1}): 3155, 1705, 1682, 1616, 1216, 1190. Anal. calcd. for $C_{32}H_{31}N_3O_4$: C 73.68, H 5.99, N 8.06%. Found: C 73.54, H 6.01, N 8.18%.

Methyl (3*S,3'*R**,4'*R**)-1''-benzyl-1',5''-dimethyl-2,2''-dioxo-4'-phenyl-1'',2''-dihydrodispiro[indoline-3,2'-pyrrolidine-3',3''-pyrrole]-4''-carboxylate (3f).** White solid (330 mg, 65%): mp 200-203 °C; ^{1}H NMR (250 MHz, CDCl$_3$): δ 7.74 (br s, 1H), 7.52 (s, 2H), 7.41-6.97 (m, 8H), 6.91 (t, *J* = 7.6 Hz, 1H), 6.79 (d, *J* = 7.6 Hz, 1H), 6.31 (d, *J* = 7.3 Hz, 2H), 5.48 (app. t, *J* = 9.0 Hz, 1H), 4.91 (d, *J* = 16.3 Hz, 1H), 4.34 (app. t, *J* = 8.4 Hz, 1H), 3.91 (d, *J* = 16.3 Hz, 1H), 3.82 (s, 3H), 3.73 (app. t, *J* = 9.6 Hz, 1H), 2.40 (s, 3H), 1.81 (s, 3H); ^{13}C NMR (63 MHz, CDCl$_3$): δ 175.1, 165.5, 155.9, 142.4, 137.7, 136.3, 129.9, 129.7, 129.0, 128.6, 127.5, 127.2, 126.3, 125.9, 125.8, 122.6, 110.2, 104.0, 78.4, 77.6, 68.7, 56.0, 51.3, 43.4, 43.0, 36.3, 13.1; IR (neat, cm^{-1}): 3139, 1708, 1684, 1614, 1252, 1218. Anal. calcd. for $C_{31}H_{29}N_3O_5$: C 73.35, H 5.76, N 8.28%. Found: C 73.13, H 5.60, N 8.14%.

Methyl (3*S,3'*R**,4'*R**)-1,1''-dibenzyl-1',5''-dimethyl-2,2''-dioxo-4'-phenyl-1'',2''-dihydrodispiro[indoline-3,2'-pyrrolidine-3',3''-pyrrole]-4''-carboxylate (3g).** Light yellow solid (448 mg, 75%): mp 113-115 °C; ^{1}H NMR (250 MHz, CDCl$_3$): δ 7.53-7.54 (m, 2H), 7.39-7.25 (m, 9H), 7.17-7.02 (m, 4H), 6.89 (t, J = 7.4 Hz, 1H), 6.58 (d, J = 7.7 Hz, 1H), 6.31 (d, J = 7.2 Hz, 2H), 5.56 (dd, J = 10.0, 8.4 Hz, 1H), 5.10 (d, J = 15.8 Hz, 1H), 4.92 (d, J = 16.3 Hz, 1H), 4.58 (d, J = 15.8 Hz, 1H), 4.37 (t, J = 8.4 Hz, 1H), 3.90 (d, J = 16.3 Hz, 1H), 3.84-3.68 (m, 4H), 2.40 (s, 3H), 1.79 (s, 3H); ^{13}C NMR (63 MHz, CDCl$_3$): δ 175.7, 175.2, 165.3, 155.3, 144.3, 137.8, 136.3, 136.1, 129.8, 129.7, 129.2, 129.0, 128.6, 127.9, 127.6, 127.5, 127.2, 126.3, 125.4, 125.2, 122.6, 109.7, 104.2, 78.4, 68.9, 56.2, 51.3, 44.0, 43.5, 43.0, 36.4, 13.1; IR (neat, cm^{-1}): 1709, 1688, 1260, 1210. Anal. calcd. for $C_{38}H_{35}N_3O_4$: C 76.36, H 5.90, N 7.03%. Found: C 76.23, H 5.81, N 7.16%.

Methyl (3*S,3'*R**,4'*R**)-1,1''-dibenzyl-4'-(4-methoxyphenyl)-1',5''-dimethyl-2,2''-dioxo-1'',2''-dihydrodispiro[indoline-3,2'-pyrrolidine-3',3''-pyrrole]-4''-carboxylate (3h)**. Light yellow solid (427 mg, 68%): mp 198-200 °C; ^{1}H NMR (250 MHz, CDCl$_3$): δ 7.37 (d, J = 8.7 Hz, 2H), 7.30-7.11 (m, 6H), 7.11-6.87 (m, 4H), 6.85-6.68 (m, 3H), 6.48 (d, J = 7.7 Hz, 1H), 6.21 (d, J = 7.2 Hz, 2H), 5.41 (dd, J = 10.2, 8.4 Hz, 1H), 5.00 (d, J = 15.8 Hz, 1H), 4.84 (d, J = 16.4 Hz, 1H), 4.48 (d, J = 15.8 Hz, 1H), 4.21 (t, J = 8.4 Hz, 1H), 3.81 (d, J = 16.4 Hz, 1H), 3.74 (s, 3H), 3.71-3.57 (m, 4H), 2.29 (s, 3H), 1.69 (s, 3H); ^{13}C NMR (63 MHz, CDCl$_3$): δ 175.7, 175.3, 165.3, 158.9, 155.2, 144.3, 136.3, 136.1, 130.8, 129.8, 129.6, 129.2, 128.9, 127.9, 127.6, 127.5, 126.3, 125.4, 125.3, 122.6, 113.9, 109.7, 104.2, 78.3, 77.6, 69.0, 56.4, 55.5, 51.3, 44.0, 42.9, 36.4, 13.0; IR (neat, cm^{-1}): 1713, 1685, 1605, 1243, 1225. Anal. calcd. for $C_{39}H_{37}N_3O_5$: C 74.62, H 5.94, N 6.69%. Found C 74.33, H 6.02, N 6.81%.

Methyl (3*S,3'*R**,4'*R**)-1''-benzyl-4'-(4-methoxyphenyl)-1',5''-dimethyl-2,2''-dioxo-1'',2''-dihydrodispiro[indoline-3,2'-pyrrolidine-3',3''-pyrrole]-4''-carboxylate (3i).** Beige solid (296 mg, 55%): mp 212-214 °C; ^{1}H NMR (250 MHz, CDCl$_3$): δ 7.57 (br s, 1H), 7.44 (d, J = 8.7 Hz, 2H), 7.33-6.97 (m, 5H), 6.98-6.68 (m, 4H), 6.31 (d, J = 7.2 Hz, 2H), 5.43 (dd, J = 10.2, 8.7 Hz, 1H), 4.93 (d, J = 16.3 Hz, 1H), 4.29 (t, J = 8.7 Hz, 1H), 3.92 (d, J = 16.3 Hz, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.70 (dd, J = 10.2, 8.7 Hz, 1H), 2.39 (s, 3H), 1.81 (s, 3H); ^{13}C NMR (63 MHz, CDCl$_3$): δ 177.9, 175.4, 165.7, 159.1, 155.9, 142.5, 136.4, 130.9, 130.0, 129.6, 129.1, 127.7, 126.5, 126.0, 122.8, 114.1, 110.3, 104.2, 78.5, 77.8, 69.0, 56.4, 55.7, 51.4, 43.1, 43.0, 36.5, 13.3; IR (neat, cm^{-1}): 3140, 1721, 1702, 1685, 1611, 1245, 1212. Anal. calcd. for $C_{32}H_{31}N_3O_5$: C 71.49, H 5.81, N 7.82%. Found: C 71.36, H 5.57, N 7.88%.

Methyl (3*S,3'*R**,4'*R**)-1''-benzyl-5-chloro-4'-(4-methoxyphenyl)-1',5''-dimethyl-2,2''-dioxo-1'',2''-dihydrodispiro[indoline-3,2'-pyrrolidine-3',3''-pyrrole]-4''-carboxylate (3j)**. Light yellow solid (418 mg, 73%): mp 181-185 °C; ^{1}H NMR (250 MHz, CDCl$_3$): δ 8.04 (br s, 1H), 7.42 (d, J = 8.8 Hz, 2H), 7.33 (d, J = 2.0 Hz, 1H), 7.23-7.01 (m, 4H), 6.84 (d, J = 8.8 Hz, 2H), 6.76 (d, J = 8.3 Hz, 1H), 6.31 (d, J = 7.1 Hz, 2H), 5.41 (dd, J = 10.0, 8.6 Hz, 1H), 4.94 (d, J = 16.3 Hz, 1H), 4.28 (app. t, J = 8.6 Hz, 1H), 3.99 (d, J = 16.4 Hz, 1H), 3.84 (s, 3H), 3.78 (s, 3H), 3.68 (dd, J = 10.0, 9.2 Hz, 1H), 2.39 (s, 3H), 1.82 (s, 3H); ^{13}C NMR (63 MHz, CDCl$_3$): δ 177.7, 175.1, 165.4, 159.0, 156.0, 141.0, 136.1, 130.7, 129.8, 129.1, 129.0, 128.2, 128.0, 127.6, 126.2, 126.2, 114.0, 111.3, 103.7, 78.3, 68.9, 56.2, 55.5, 51.4, 42.9, 36.3, 31.4, 13.2; IR (neat, cm^{-1}): 3199, 1721, 1688, 1605, 1245, 1207. Anal. calcd. for $C_{32}H_{30}ClN_3O_5$: C 67.19, H 5.29, N 7.35%. Found: C 67.02, H 5.34, N 7.30%.

Methyl (3*S,3'*R**,4'*R**)-1''-benzyl-5-iodo-4'-(4-methoxyphenyl)-1',5''-dimethyl-2,2''-dioxo-1'',2''-dihydrodispiro[indoline-3,2'-pyrrolidine-3',3''-pyrrole]-4''-carboxylate (3k).** Pale brown solid (331 mg, 50%): mp 141-143 °C; ^{1}H NMR (250 MHz, CDCl$_3$): δ 8.35 (br s, 1H), 7.42 (d, J = 1.8 Hz, 1H), 7.32 (dd, J = 8.2, 1.8 Hz, 1H), 7.21 (d, J = 8.8 Hz, 2H), 7.00-6.80 (m, 3H), 6.63 (d, J = 8.8 Hz, 2H), 6.44 (d, J = 8.2 Hz, 1H), 6.10 (d, J = 7.0 Hz, 2H), 5.21 (dd, J = 10.0, 8.6 Hz, 1H), 4.77 (d, J = 16.4 Hz, 1H), 4.07 (app. t, J = 8.6 Hz, 1H), 3.76 (d, J = 16.4 Hz, 1H), 3.63 (s, 3H), 3.54 (s, 3H), 3.48 (dd, J = 10.0, 9.1 Hz, 1H), 2.18 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (63 MHz, CDCl$_3$): δ 177.5, 175.2, 165.4, 159.0, 156.1, 142.3, 138.6, 136.1, 134.5, 130.7, 129.1, 129.0, 128.5, 127.6, 126.2, 113.9, 112.6, 103.6, 85.1, 78.2, 68.9, 56.3, 55.6, 51.4, 42.8, 42.8, 36.4, 13.3; IR (neat, cm^{-1}): 3164, 1714, 1694, 1671, 1245, 1176. Anal. calcd. for $C_{32}H_{30}IN_3O_5$: C 57.93, H 4.56, N 6.33%. Found: C 57.75, H 4.42, N 6.46%.

Methyl (3*S,3'*R**,4'*R**)-1''-benzyl-4'-(4-methoxyphenyl)-1',5,5''-trimethyl-2,2''-dioxo-1'',2''-dihydrodispiro[indoline-3,2'-pyrrolidine-3',3''-pyrrole]-4''-carboxylate (3l)**. Light yellow solid (298 mg, 54%): mp 213-215 °C; ^{1}H NMR (250 MHz, CDCl$_3$): δ 7.41 (br s, 1H), 7.34 (d, J = 8.7 Hz, 2H), 7.10-6.85 (m, 5H), 6.79-6.68 (m, 2H), 6.57 (d, J = 7.9 Hz, 1H), 6.22 (d, J = 7.1 Hz, 2H), 5.32 (dd, J = 10.3, 8.6 Hz, 1H), 4.78 (d, J = 16.3 Hz, 1H), 4.18 (t, J = 8.6 Hz, 1H), 3.88 (d, J = 16.3 Hz, 1H), 3.74 (s, 3H), 3.72 (s, 3H), 3.59 (dd, J = 10.3, 8.6 Hz, 1H), 2.29 (s, 3H), 2.16 (s, 3H), 1.70 (s, 3H); ^{13}C NMR (63 MHz, CDCl$_3$): δ 177.7, 175.3, 165.5, 158.9, 155.6, 139.8, 136.3, 132.1, 130.7, 130.1, 129.5, 128.9, 127.5, 126.6, 126.2, 113.9, 109.8, 104.1, 78.3, 77.6, 68.8, 56.3, 55.5, 51.3, 42.9, 42.8, 36.3, 21.5, 13.1; IR (neat, cm^{-1}): 3162.5, 1706.6, 1687.8, 1616.8, 1247.0, 1217.0; IR (neat, cm^{-1}): 3164, 1714, 1694, 1671, 1245, 1176. Anal. calcd. for $C_{33}H_{33}N_3O_5$: C 71.85, H 6.03, N 7.62%. Found: C 71.91, H 5.97, N 7.58%.

Methyl (3*S,3'*R**,4'*R**)-1''-benzyl-4'-(4-chlorophenyl)-1',5''-dimethyl-2,2''-dioxo-1'',2''-dihydrodispiro[indoline-3,2'-pyrrolidine-3',3''-pyrrole]-4''-carboxylate (3m).** White solid (423 mg, 78%): mp 118-120 °C; ^{1}H NMR (250 MHz, CDCl$_3$): δ 7.45 (d, J = 8.5 Hz, 2H), 7.37 (br s, 1H), 7.29-7.03 (m, 7H), 6.92 (td, J = 7.6, 0.6 Hz, 1H), 6.78 (d, J = 7.6 Hz, 1H), 6.39-6.20 (m, 2H), 5.45 (dd, J = 10.1, 8.3 Hz, 1H), 4.93 (d, J = 16.3 Hz, 1H), 4.28 (t, J = 8.3 Hz, 1H), 3.90 (d, J = 16.3 Hz, 1H), 3.83 (s, 3H), 3.79-3.66 (m, 1H), 2.40 (s, 3H), 1.82 (s, 3H); ^{13}C NMR (63 MHz, CDCl$_3$): δ 176.6, 174.1, 164.3, 154.9, 141.3, 135.2, 135.1, 132.1, 130.1, 129.0, 128.1, 127.7, 126.8, 125.2, 124.7, 121.7, 109.3, 102.7, 77.4, 67.6, 55.0, 50.4, 42.0, 41.8, 35.2, 30.4, 12.1; IR (neat, cm^{-1}): 3142, 1724, 1705, 1686, 1615, 1286, 1209. Anal. calcd. for $C_{31}H_{28}ClN_3O_4$: C 68.69, H 5.21, N 7.75%. Found: C 68.57, H 5.07, N 7.81%.

Methyl (3*S,3'*R**,4'*R**)-1''-benzyl-4'-(4-bromophenyl)-1',5''-dimethyl-2,2''-dioxo-1'',2''-dihydrodispiro[indoline-3,2'-**

pyrrolidine-3',3''-pyrrole]-4''-carboxylate (3n). Pale brown solid (516 mg, 88%): mp 222 °C; ^{1}H NMR (250 MHz, DMSO-d_6): δ 10.34 (br s, 1H), 7.50 (d, *J* = 8.6 Hz, 2H), 7.33 (d, *J* = 8.6 Hz, 2H), 7.24-7.00 (m, 5H), 6.86 (td, *J* = 7.6, 0.9 Hz, 1H), 6.74 (d, *J* = 7.6 Hz, 1H), 6.32 (d, *J* = 6.8 Hz, 2H), 5.32 (dd, *J* = 10.1, 8.2 Hz, 1H), 4.72 (d, *J* = 16.6 Hz, 1H), 4.25 – 3.95 (m, 2H), 3.70 (s, 3H), 3.57-3.46 (m, 1H), 2.15 (s, 3H), 1.71 (s, 3H); ^{13}C NMR (63 MHz, DMSO-d_6): δ 176.6, 174.4, 164.5, 154.5, 143.7, 137.1, 136.6, 131.4, 131.3, 129.9, 128.6, 127.3, 125.9, 125.1, 124.8, 121.6, 120.5, 110.0, 103.2, 77.5, 67.7, 51.2, 42.0, 41.9, 35.5, 31.1, 12.5; IR (neat, cm^{-1}): 3141, 1724, 1704, 1686, 1614, 1285, 1208. Anal. calcd. for $C_{31}H_{28}BrN_3O_4$: C 63.49, H 4.81, N 7.16%. Found: C 63.62, H 4.77, N 7.05%.

Methyl (1'*R,2'*R**,3*S**,7a'S)-1''-butyl-5''-methyl-2,2''-dioxo-1'-phenyl-1'',2'',5',6',7',7a'-hexahydro-1'*H*-dispiro[indoline-3,3'-pyrrolizine-2',3''-pyrrole]-4''-carboxylate (4a).** Light yellow solid (210 mg, 42%): mp 156-158 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.81 (br s, 1H), 7.46 (d, *J* = 6.5 Hz, 2H), 7.38 (d, *J* = 7.5 Hz, 1H), 7.28-7.09 (m, 4H), 6.90 (t, *J* = 7.5 Hz, 1H), 6.71 (d, *J* = 7.7 Hz, 1H), 4.91 (s, 2H), 3.81 (s, 3H), 3.34-3.16 (m, 1H), 3.11-2.95 (m, 1H), 2.88 (t, *J* = 7.1 Hz, 1H), 2.81-2.64 (m, 1H), 2.31-2.00 (m, 4H), 1.94 (s, 3H), 1.22-1.05 (m, 2H), 1.04-0.88 (m, 2H), 0.80 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 178.7, 175.8, 165.8, 154.8, 141.4, 137.8, 129.4, 129.3, 128.4, 127.1, 126.0, 122.5, 109.8, 104.2, 77.3, 73.2, 68.7, 51.2, 49.7, 47.9, 39.8, 32.4, 31.0, 30.5, 20.1, 14.1, 12.7; IR (neat, cm^{-1}): 3138, 1707, 1687, 1615, 1254, 1205. Anal. calcd. for $C_{30}H_{33}N_3O_4$: C 72.12, H 6.66, N 8.41%. Found: C 71.98, H 6.55, N 8.46%.

Ethyl (1'*R,2'*R**,3*S**,7a'S)-1''-butyl-5''-methyl-2,2''-dioxo-1'-phenyl-1'',2'',5',6',7',7a'-hexahydro-1'*H*-dispiro[indoline-3,3'-pyrrolizine-2',3''-pyrrole]-4''-carboxylate (4b).** Light yellow solid (195 mg, 38%): mp 155-157 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.58 (br s, 1H), 7.46 (d, *J* = 6.9 Hz, 2H), 7.35 (d, *J* = 7.5 Hz, 1H), 7.28-7.00 (m, 4H), 6.87 (t, *J* = 7.7 Hz, 1H), 6.66 (d, *J* = 7.7 Hz, 1H), 4.91 (s, 1H), 4.99-4.77 (m, 2H), 4.32 (m, 1H), 4.16 (m, 1H), 3.29-3.13 (m, 1H), 3.06-2.91 (m, 1H), 2.85 (t, *J* = 7.5 Hz, 1H), 2.70 (dd, *J* = 16.4, 7.9 Hz, 1H), 2.26-1.96 (m, 4H), 1.91 (s, 3H), 1.39 (t, *J* = 7.1 Hz, 3H), 1.18-1.01 (m, 2H), 1.01-0.83 (m, 2H), 0.76 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 178.6, 175.8, 165.4, 154.5, 141.4, 137.8, 129.4, 128.4, 128.0, 127.1, 126.0, 122.5, 109.8, 104.2, 77.3, 73.3, 68.7, 60.6, 49.7, 47.8, 39.8, 32.4, 31.0, 30.5, 30.1, 20.1, 14.6, 14.1, 12.6; IR (neat, cm^{-1}): 3190, 1708, 1681, 1612, 1249, 1203. Anal. calcd. for $C_{31}H_{35}N_3O_4$: C 72.49, H 6.87, N 8.18%. Found: C 72.33, H 6.90, N 7.97%.

Conclusions

A sequential reaction between primary amines, β-dicarbonyl compounds and α-bromoesters in the presence of indium trichloride as a Lewis acid catalyst, which was performed under microwave-assisted, solvent-free conditions, constitutes the first multicomponent synthesis of 2-pyrrolin-5-ones and proceeds *via* a Hantzsch-type mechanism. In spite of their simplicity and potential importance in drug discovery, these compounds are not easily synthesized by the few previously known methods. Their ready preparation by our method allowed their use as synthetic building blocks, both in target-oriented and diversity-oriented synthesis contexts. Thus, we devised a two-step route to compound **2**, which had previously been proposed as a suitable candidate for HIV integrase inhibition on the basis of computational studies. The versatility of 2-pyrrolin-5-ones was further verified by their use in a diversity-oriented synthesis context, leading to a library of highly functionalized bispiro compounds. The overall process leading to these compounds involved the generation of six bonds and two cycles over three steps, two of which are multicomponent, and the fully controlled generation of up to four stereocenters, including two quaternary ones.

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Textual Abstract

The combination of two multicomponent reactions, i.e. a Hantzsch-type synthesis of 2-pyrrolin-5-ones and a 1,3-dipolar cycloaddition generated complex spirocyclic systems.