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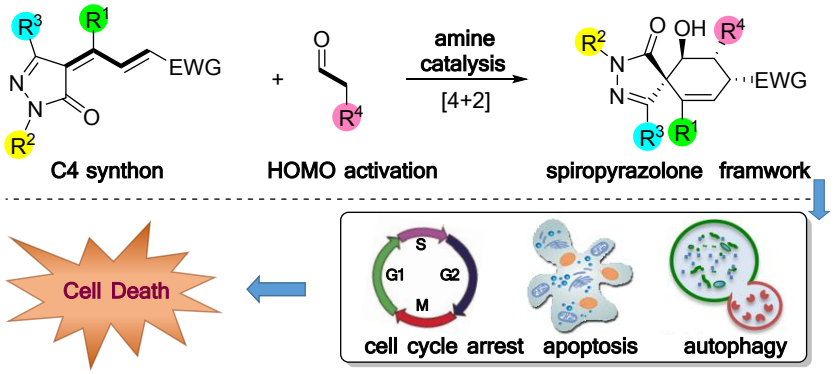
Stereoselective assembly of multifunctional spirocyclohexene pyrazolones that induce autophagy-dependent apoptosis in colorectal cancer cells

Xiang Li,[†] Fei-Yu Chen,[†] Jing-Wen Kang,[†] Jin Zhou,[†] Cheng Peng,*[†] Wei Huang,[†] Mu-Ke Zhou,[‡] Gu He*[‡] and Bo Han*[†]

[†] *State Key Laboratory of Southwestern Chinese Medicine Resources, School of Pharmacy, Chengdu University of Traditional Chinese Medicine, Chengdu 611137, China. E-mail: pengcheng@cdutcm.edu.cn or hanbo@cdutcm.edu.cn*

[‡] *State Key Laboratory of Biotherapy and Department of Dermatology, West China Hospital, Sichuan University and Collaborative Innovation Center for Biotherapy, Chengdu, 610041, China. E-mail: hegu@scu.edu.cn*



Abstract: Enantio- and diastereoselective synthesis of multifunctional spiropyrazolone scaffolds has been achieved using secondary amine-catalyzed [4+2] annulations of α,β,γ,δ-unsaturated pyrazolones with aldehydes. The pyrazolone substrates serve as C4 synthons to produce six-membered, carbocycle-based, chiral spiropyrazolone derivatives. The synthesized chiral compounds showed potent toxicity against a panel of cancer cell lines. The most potent compound **3h** induced cell cycle arrest and macroautophagy in HCT116 colorectal cancer cells, triggering autophagy-dependent apoptotic cell death.

Introduction

The unique combination of a lactam functionality and two adjacent nitrogen atoms makes the pyrazolone framework a privileged structure in medicinal chemistry and drug discovery.[1] Of particular interest are spirocyclohexane(ene) pyrazolones, which contain a six-membered chiral

carbocyclic ring and show attractive biological activities.[2] Cyclohexane(ene)-fused spiropyrazolones with multiple functional groups show insecticidal, antibacterial, analgesic, anti-inflammatory and antitumor properties (Figure. 1). Since the stereochemistry of spirocyclic pyrazolones strongly affects their antitumor activity,[3] convenient and efficient methods to asymmetrically synthesize spirocyclohexane(ene) pyrazolones are highly desirable.[4]

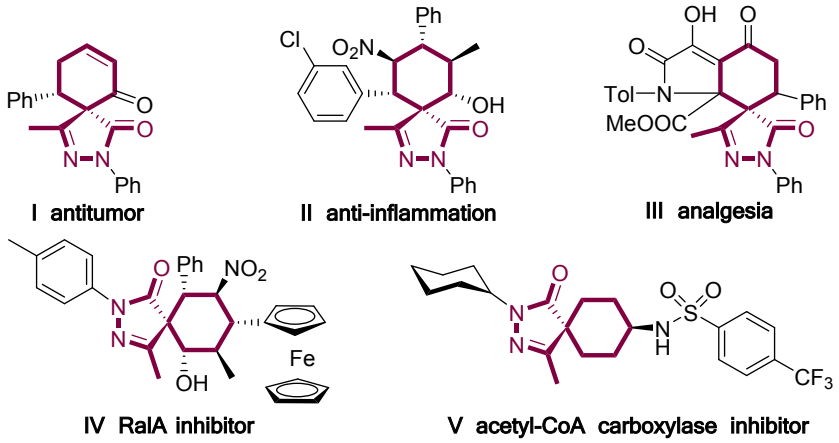
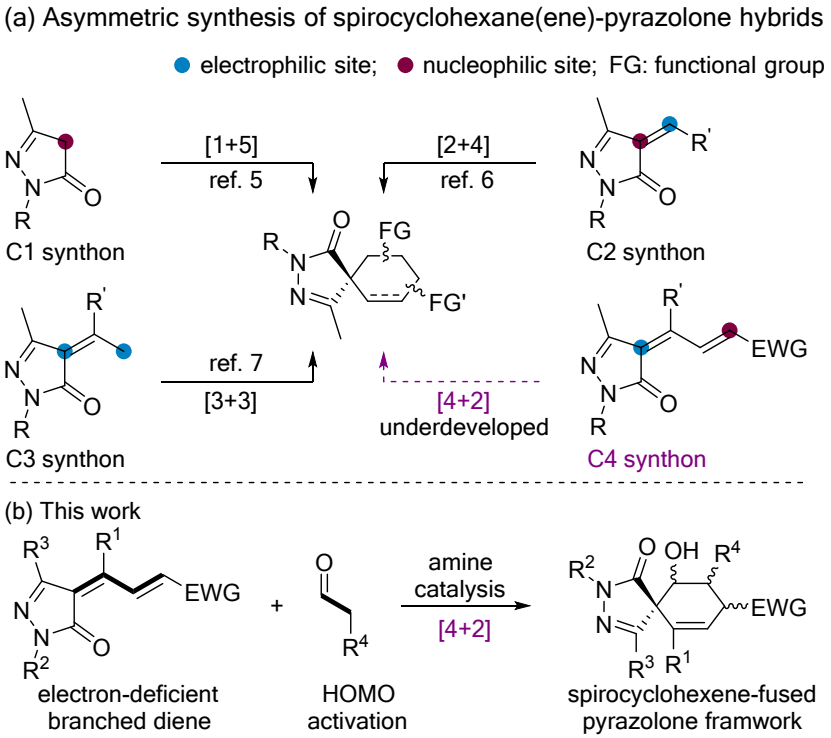


Figure 1. Selected bioactive compounds containing a cyclohexane(ene)-fused spiropyrazolone skeleton. RalA, Ras-like proto-oncogene A.

Pyrazolin-5-one substrates have shown great potential in asymmetric organocatalytic reactions to construct six-membered carbocycle-based chiral spiropyrazolone scaffolds (Scheme 1a).[5-7] The simple pyrazolin-5-one (edaravone) serves as a nucleophilic C1 synthon in domino [**1**+2+3] or [**1**+5] cyclizations.[5] The α-arylidene pyrazolinones serve as versatile electrophilic C2 synthons in various asymmetric [**2**+2+2] or [**2**+4] annulations,[6] while α,β-unsaturated pyrazolones bearing a γ-hydrogen have been exploited in [**3**+3] cyclizations involving vinylogous γ-additions.[7] However, few reports exist of catalytic asymmetric [**4**+2] cyclizations using pyrazolone substrates as four-carbon building blocks. This led us to search for suitable C4 surrogates and to develop novel, alternative strategies to synthesize pharmacologically interesting spiropyrazolone derivatives, as part of our continuing interest in combining asymmetric synthesis and medicinal chemistry.[8]

We designed an amine-catalyzed asymmetric [4+2] annulation of α,β,γ,δ-unsaturated pyrazolone **1** with aldehyde **2** to produce the target framework (Scheme 1b). In this reaction, the α,β,γ,δ-unsaturated pyrazolone substrate **1** serves as the electron-deficient C4 building block



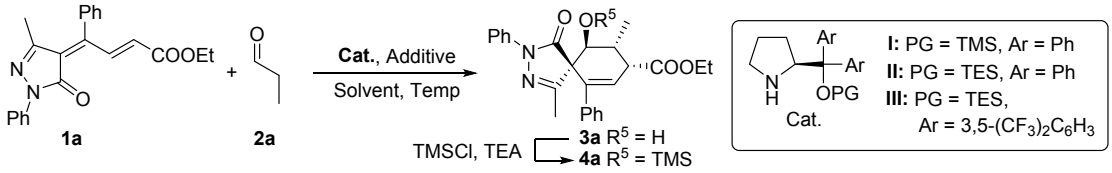
Scheme 1. Strategies to construct six-membered carbocycle-based chiral spiropyrazolone scaffolds.

as well as branched diene for spiro-construction,[9] while the aldehyde **2** is activated via a HOMO-raising strategy.[10] The resulting spirocyclohexene-pyrazolone hybrids can provide a chiral spirocycle library for bioactive screening as part of the combinatorial pharmacophore strategy, which can be effective for lead discovery.

RESULTS AND DISCUSSION

Initially, the reaction of α,β,γ,δ-unsaturated pyrazolone **1a** with n-propanal **2a** was employed as a model reaction to probe the validity of the proposed organocatalytic annulation reaction. In the presence of Hayashi-Jørgensen catalyst **Cat. I** in toluene at 25 °C, the desired spirocyclic product was isolated with good yield and good ee value albeit in moderate dr value (Table 1, entry 1). In efforts to improve stereoselectivity as well as yield, other catalysts were evaluated; however, only a slightly increasing ee and dr value was observed (entry 2 and 3). Then we attempted to investigate other various reaction parameters such as solvent, additive, and reaction temperature. We found that the properties of different solvents showed significantly

Table 1. Optimization of the model reaction[a]



Entry	**Cat.**	Solvent[e]	Additive	Temp (°C)	Yield (%)[b]	dr[c]	ee (%)[d]
1	**I**	Tol	BzOH	25	51	62:38	43
2	**II**	Tol	BzOH	25	52	62:38	45
3	**III**	Tol	BzOH	25	54	65:35	53
4	**III**	CH_2Cl_2	BzOH	25	62	70:30	66
5	**III**	$CHCl_3$	BzOH	25	60	68:32	68
6	**III**	MeCN	BzOH	25	76	73:27	76
7	**III**	THF	BzOH	25	76	75:25	80
8	**III**	THF	2-FBzOH	25	74	75:25	78
9	**III**	THF	3-NO_2BzOH	25	78	72:28	76
10	**III**	THF	AcOH	25	74	73:27	78
11	**III**	THF	-	25	63	70:30	68
12	**III**	THF	BzOH	0	76	80:20	90
13	**III**	**THF**	**BzOH**	**-20**	**75**	**84:16**	**97**
14	**III**	THF	BzOH	-30	70	84:16	96
15[f]	**III**	THF	BzOH	-20	67	84:16	94

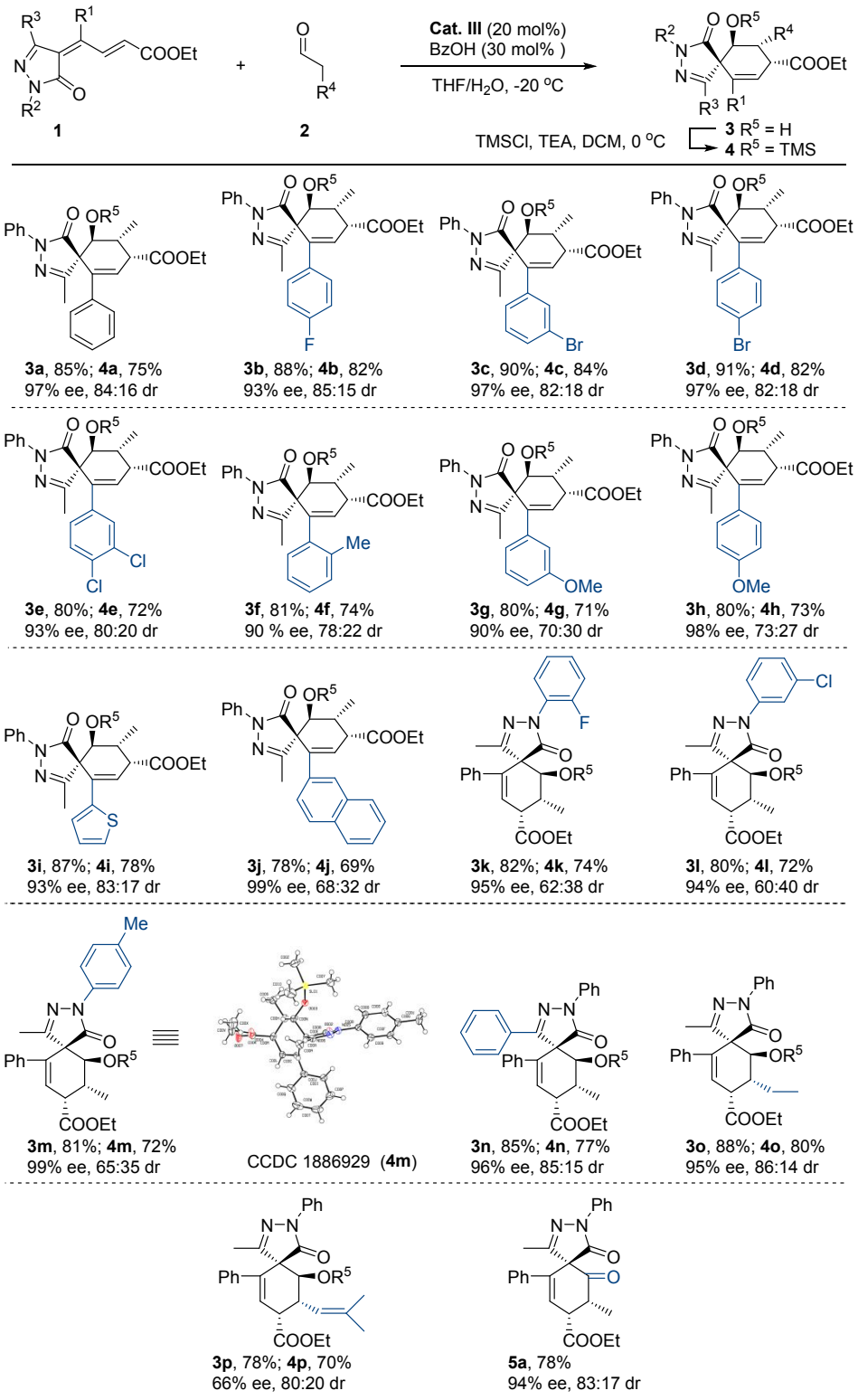
[a] Reactions were performed with **1a** (0.15 mmol), **2a** (0.30 mmol), catalyst (20 mol%) and acidic additive (30 mol%) in 1.5 mL of solvent at 25 °C. [b] Yield of isolated major isomer **4a** over two steps. [c] Calculated based on ^{1}H NMR analysis of the crude reaction mixture. [d] Determined by chiral HPLC analysis of the major diastereoisomer. [e] The ratio of solvent/H_2O was 20:1 in v/v. [f] 10 mol% catalyst was used.

impact on stereoselectivity as well as yield (entry 4-7) and using tetrahydrofuran delivered the desirable product with 80% ee from 53% ee and 75:25 dr from 65:35 dr (entry 7). Various acid additives were also investigated, and benzoic acids with an electron-withdrawing group on the

aromatic ring or acetic acid slightly affected stereoselectivity of the product while retaining good yield (entry 8-10). Besides, inferior stereoselectivity of the reaction was observed without the promotion of acid additive (entry 11). After lowering the reaction temperature in order to enhance diastereoselectivity and enantioselectivity, an excellent 97% ee and 84:16 dr was provided when the reaction was conducted at -20 ^{o}C (entry 12-14). Reducing the load of catalyst decreased the yield of the reaction with maintaining in high stereoselectivity (entry 15).

These optimized conditions were used to investigate substrate scope with various kinds of α,β,γ,δ-unsaturated pyrazolones **1** (Scheme 2). The reaction tolerated a broad range of substrates with diverse electronic and steric properties, affording the corresponding products **4** in satisfying yields (69-84%) with good to high diastereoselectivities (up to 86:14 d.r.) and excellent enantioselectivites (up to 99% ee). For example, the reaction tolerated electron-deficient and -rich substituents on the aryl ring at position R^1 at *ortho*-, *meta*-, and *para*-positions of **1**, giving the spirocyclohexene-pyrazolones **4a**-**h** in yields of 71-84% with up to 98% ee and up to 85:15 dr. Also suitable as substrates were α,β,γ,δ-unsaturated pyrazolones containing thienyl or 2-naphthyl groups, which provided the desired products **4i** and **4j** in reasonable yield, although the 2-naphthyl moiety led to low diastereoselectivity. Changing the electronic properties of the functional groups at position R^2 slightly affected the enantioselectivity of the reaction in a few cases (**4k**-**m**), although it did reduce dr values. The absolute configuration of **4m** was assigned based on single-crystal X-ray diffraction analysis (CCDC 1886929), and the configurations of products **3** and **4** were assigned by analogy.[11] Impressively, the reaction performed quite well in the presence of a bulky phenyl group at position R^3, generating **4n**. Switching the aldehyde **2** from propanal to n-butanal or 4-methyl-2-pentenal led to good yields and diastereoselectivities for products **4o** and **4p**, although enantioselectivity was only moderate for the latter product. Treating **3a** with PCC generated the oxidation product **5a** in excellent yield. This product can diversify the framework of bioactive spirocyclohexene-pyrazolones. Further modifying ester group of **1** with phenyl group failed to deliver the target products due to the inert reactivity of substrates. Moreover, we successfully obtained some TMS-protected diastereoisomers of **4'** with moderate dr values. The relative configuration of minor diastereoisomer **4k'** was assigned based on single-crystal X-ray

diffraction analysis (CCDC 1910043), and the configurations of products **4'** were assigned by analogy (see details in ESI).[12]



Scheme 2. Substrate scope of the annulation reaction. Yield was calculated from the isolated diastereomer of **3** or **4**; dr values, from ^{1}H NMR analysis of the crude mixture of **3** and **4**; and ee values,

from chiral HPLC analysis of major isomer **4**. Compound **3a** was oxidized with PCC in CH_2Cl_2 at 40 °C for 6 h to yield **5a**.

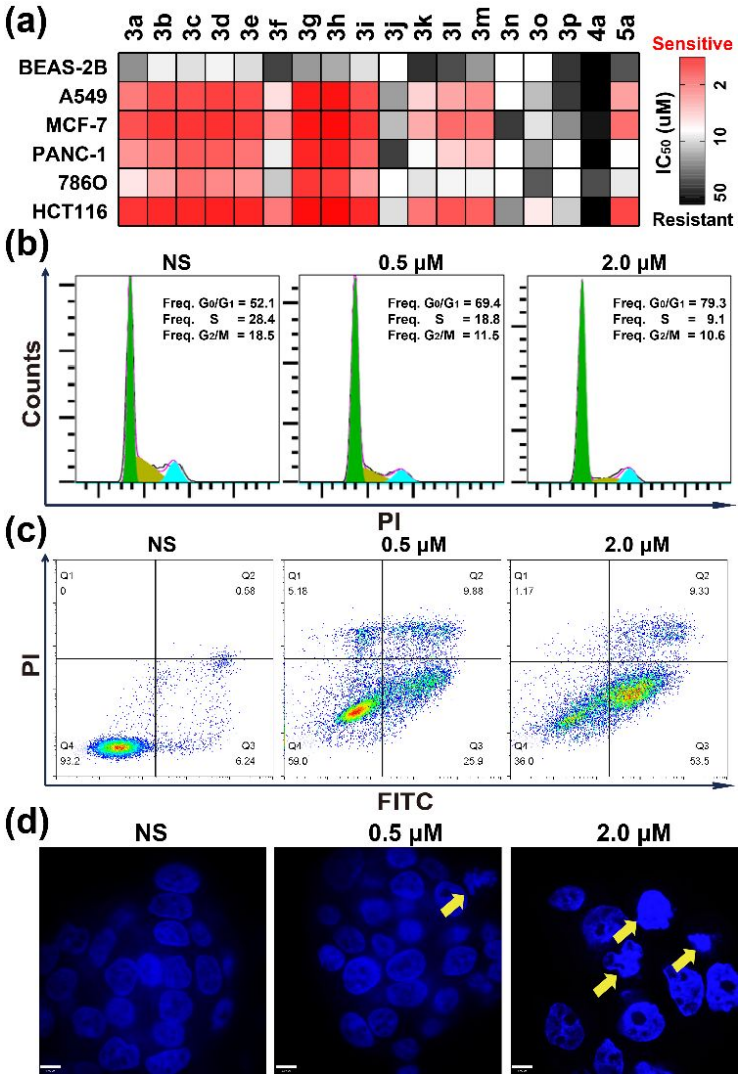


Figure 2. (a) Heat map of mean half maximal inhibitory concentrations (IC_{50}) of compounds **3a**–**3p**, **4a** and **5a** against a panel of normal or cancer cell lines. Mean values were determined from triplicate experiments. (b) Cell cycle analysis of HCT116 cells incubated with 0.5 or 2.0 μM **3h** for 24 h. (c) Apoptosis levels in HCT116 cells incubated with 0.5 or 2.0 μM **3h** for 24 h, based on dual staining with annexin-V/propidium iodide followed by flow cytometry. (d) Nuclear morphology in HCT116 cells incubated with 0.5 or 2.0 μM **3h** for 24 h, followed by Hoechst 33258 staining. Scale bar: 6 μm.

Next we wanted to screen the cyclohexene-fused spiropyrazolone products of our reaction for potential bioactivity.[13] According to Lipinski's rules, **3** showed a more favorable lipo-hydro partition coefficient and number of hydrogen bond donors and acceptors than **4**.[14] Therefore we mainly focused our bioactivity screening efforts on **3**. Compounds **3a-3p**, **4a** and **5a** showed various degrees of toxicity against a panel of cancer cell lines without remarkable effects on

BEAS-2B human bronchial epithelial cells (Figure 2a, Table S1). Several modifications substantially reduced this cytotoxicity: protecting the OH group of **3a** with TMS (**4a**),

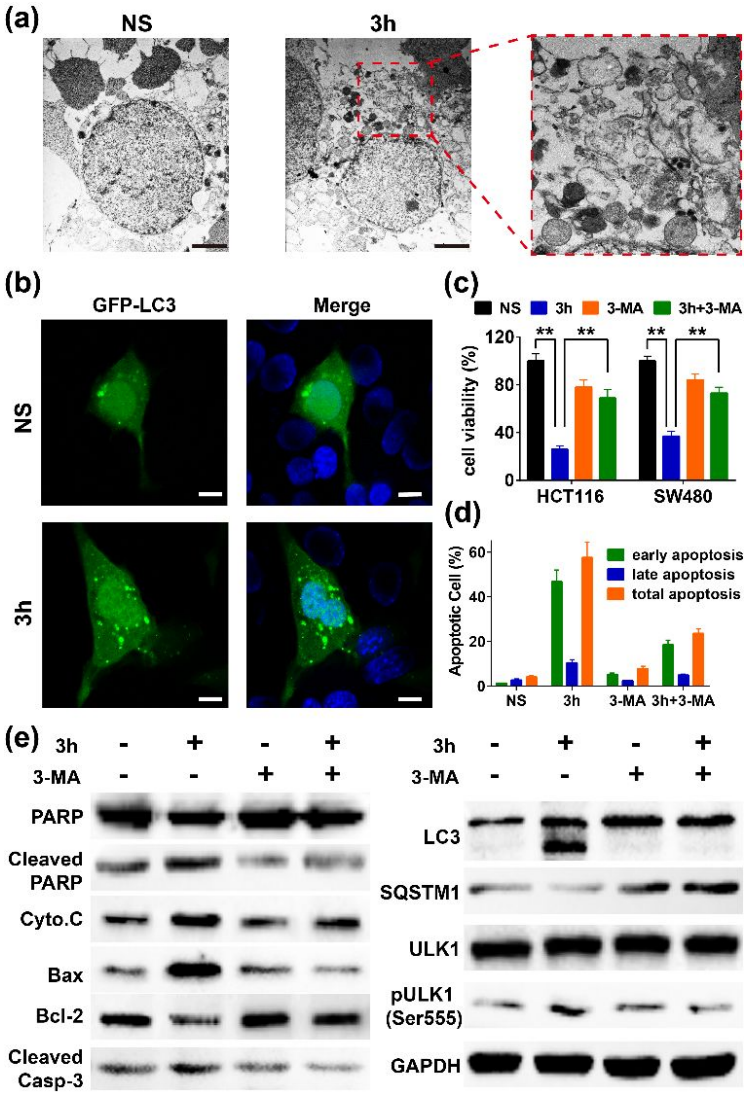


Figure 3. (a) Analysis of autophagic vacuoles in HCT116 cells after incubation with 0.5 μM 3h for 24 h. Cells were analyzed using transmission electron microscopy. Scale bar: 1 μm. (b) HCT116 cells were transfected with GFP-LC3 plasmid, then incubated with 0.5 μM 3h for 24 h. Nuclei were visualized using propidium iodide staining, while autophagosomes were imaged as GFP-LC3 puncta under a fluorescence microscope. Scale bar: 6 μm. (c) HCT116 cells were treated with 2.0 μM 3h with or without 1 mM 3-MA, then cell viability was assayed using the MTT method. ** $p < 0.01$. (d) HCT116 cells were treated with 2.0 μM 3h with or without 1 mM 3-MA, then apoptotic cells were quantified based on dual staining with annexin V and propidium iodide. (e) HCT116 cells were incubated with 2.0 μM 3h for 24 h with or without 1 mM 3-MA, then levels of apoptosis- and autophagy-related proteins were assessed using Western blotting.

introducing a 2-naphthyl at R^1 (**3j**), introducing a phenyl group at R^3 (**3n**) or adding a long-chain alkyl group at R^4 (**3o**, **3p**). In contrast, oxidizing the hydroxyl group to a ketone (**5a**) only slightly reduced toxicity. Substituting an *N*-phenyl group at R^2 on the pyrazolone moiety (**3k**-**3m**) did not improve cytotoxicity. In contrast, adding an *m*- or *p*-methoxyl-substituted phenyl group at R^1 (**3g** and **3h**) did improve toxicity.

In order to begin to identify potential mechanisms of **3h** cytotoxicity, we focused on the compound's effects on cell cycle progression and apoptosis in HCT116 colorectal cancer cells. After 24 h incubation, **3h** induced cell cycle arrest at G0/G1 phase in a dose-dependent manner (Figure 2b). The compound also induced apoptotic cell death, based on staining with annexin-V/propidium iodide (Figure 2c) and altered nuclear morphology as revealed by Hoechst 33258 staining (Figure 2d).

In addition, 24 h incubation with 0.5 μM **3h** potently induced macroautophagic vacuole formation in HCT116 cells expressing GFP-LC3. These vacuoles were visualized using transmission electron microscopy (Figure 3a) and fluorescence microscopy, which detected GFP-LC3 puncta in cytoplasm (Figure 3b).[15] To examine whether this macroautophagy may help explain the observed cytotoxicity of **3h**, we incubated HCT116 or SW480 cells with **3h** alone or in combination with the autophagy inhibitor 3-methyladenine (3-MA). This inhibitor reversed the ability of **3h** to induce cytotoxicity and apoptosis, to up-regulate expression of proapoptotic PARP, Caspase-3, Bax and cytochrome c, and to down-regulate anti-apoptotic Bcl-2. Similarly, 3-MA reversed **3h**-induced changes in LC3 cleavage, SQSTM1 degradation and ULK1 phosphorylation at Ser555 (Figure 3c-3e).[16] These results suggest that **3h** induces autophagy-dependent apoptotic cell death in HCT116 colorectal cancer cells.[17]

CONCLUSIONS

Here we report a highly enantioselective organocatalyzed [4+2] cyclization of α,β,γ,δ-unsaturated pyrazolones and aldehydes that facilely delivers a variety of drug-like spirocyclohexene pyrazolones bearing contiguous stereogenic centers and multiple functional groups. A small preliminary library of these pyrazolones was found to contain compounds that

suppressed proliferation in a panel of cancer cell lines. The most potent compound, **3h**, was found to arrest HCT116 cells in G0/G1 phase and induce macroautophagy and apoptosis in a dose-dependent manner. These anticancer effects of **3h** were reversed by the autophagy inhibitor 3-MA, suggesting that **3h** exerts its effects by stimulating autophagy-dependent apoptosis. These results demonstrate the potential of our cyclization procedure for generating novel spiropyrazolone derivatives that can kill cancer cells by inducing programmed cell death. Further studies to explore novel chiral small molecules against colorectal cancer are ongoing in our laboratory.

EXPERIMENTAL SECTION

General information

NMR data were obtained for ^{1}H at 400 MHz and for ^{13}C at 100 MHz, or for ^{1}H at 600 MHz and for ^{13}C at 150 MHz. Chemical shifts were reported in parts per million (ppm) using tetramethyl silane as internal standard with solvent resonance in $CDCl_3$ or DMSO-d_6. Enantiomeric ratios were determined by comparing HPLC analyses of products on chiral columns with results obtained using authentic racemates. UV detection was performed at 254 nm. ESI-HRMS spectra were measured with a Q-TOF instrument. Column chromatography was performed on a silica gel (200-300 mesh) using an eluent of ethyl acetate and petroleum ether. TLC was performed on glass-backed silica plates; products were visualized using UV light. Melting points were determined on a Mel-Temp apparatus.

Cell culture and cellular proliferation assay

The human lung cancer cell line A549, human breast cancer cell line MCF-7, human pancreatic cancer cell line PANC-1, human renal cell carcinoma cell line 786O and human colorectal cell line HCT116 were incubated under sterile conditions at 37 ℃ and were maintained in a humidified atmosphere 5% (vol/vol) CO_2 with RPMI-1640 or DMEM medium containing 10% fetal bovine serum (GIBCO, Waltham, MA, USA). MTT assay was performed to evaluate the

cellular proliferation inhibitory activities of tested compounds by a panel of cancer cell lines. In general, cells were seeded into 96-well plates and treated with a series of concentration of test drugs for 24 h. The MTT reagent (5 mg/ml) was added per well for 3 h at 37 °C. After that, the MTT was removed and 150 μL DMSO was added to dissolve the formazan crystals. Then, optical density (OD) was measured at 570 nm of the solution. The control group consisted of untreated cells. The percentage of cell viability averaged from three individual experiments.

Cell cycle, apoptosis assay by Flow Cytometry (FCM) and fluorescent microscopy

HCT116 cells were seeded in 6-well plates for 12 h, and then treated with compound **3h** (0.5 or 2 μM, respectively) or vehicle (DMSO) for 16 h. Cells were collected, then fixed with 75% ice-cold ethanol and stored at -20 °C for 1 h. After centrifugation, the cells were washed with ice-cold PBS twice, then stained with PI at 4 °C for 20 min in the dark. Cell cycle analysis was performed in an FACS Calibur flow cytometer. Apoptosis induction assay processed by FACS in HCT116 cells treated with compound **3h**. HCT116 cells treated with compound **3h** or saline (control) were gently trypsinized without EDTA and centrifuged at 2000 rpm for 5 minutes. Then, the harvested cells were washed with 1.0 ml ice cold PBS and re-suspended in 500 μL binding buffer, and incubated with 5 μL of Annexin V-FITC and 5 μL of propidium iodide (PI) for 15 min at room temperature. Followed by FCM (BD FACS Calibur, BD, USA) using the FL1 channel for Annexin V-FITC and the FL2 channel of PI. Both early apoptotic (Annexin V+/PI-) and late apoptotic (Annexin V+/PI+) cells are included in the cell assay of apoptosis.

In separate experiments, the extent of apoptosis was assessed based on alteration of nuclear morphology detected using the nucleus-specific dye Hoechst 33342 (Keygen, Nanjing, China). Cells were seeded into 6-well plates containing coverslips (4×10^5 cells per well), cultured for 24 h, then treated with compound **3h** (0.5 or 2 μM, respectively) or vehicle (DMSO) for 24 h. Cells were then washed twice with PBS, fixed with 4% paraformaldehyde for 20 min at room temperature, stained with Hoechst 33342 (5 μg/ml) in the dark at 37 °C for 30 min and analyzed using inverted fluorescence microscopy (TE-2000, Nikon, Japan). Cells containing uniformly stained nuclei were scored as healthy, while cells containing condensed or fragmented nuclei were scored as apoptotic.

Autophagy assays

HCT116 cells were transfected with a plasmid encoding a fusion of GFP with the C-terminal domain of LC3 protein (also known as microtubule-associated protein 1A/1B light chain 3B). Transfected cultures were treated with compound **3h** (0.5 μM) and observed using fluorescence microscopy (Axio Observer A1, Zeiss, Germany). Autophagy-positive cells were defined as those containing GFP-LC3 puncta. The HCT116 cells were treated with compound **3h** (0.5 μM) for 24 h, collected and washed with ice-cold PBS, then fixed with 4% glutaraldehyde in 0.1 M sodium cacodylate for 2 h. Cells were then post-fixed with 1% OsO4 for 1.5 h, washed, dehydrated and embedded in Epon-Araldite resin. Ultrathin sections (80 nm) were prepared, stained with 3% aqueous uranyl acetate for 1 h, and counterstained with 0.3% lead citrate. Sections were analyzed using transmission electron microscopy (HT7700, Hitachi, Japan).

Western blot analysis

The compound **3h** treated HCT116 cells with or without combination of autophagy inhibitor 3-MA were harvested and washed with cold 1×PBS. Total cell lysates were prepared in lysis RIPA buffer (Invitrogen, CA, USA) on ice for 30 min, followed by centrifugation at 13000 rpm for 30 min at 4 ^{o}C. After collecting supernatant, protein concentration was determined by a bicinchoninic acid protein assay kit (Thermo, USA). The protein was resolved on a 10-15% SDS-polyacrylamide gel, electro blotted onto nitrocellulose membranes, and then incubated with proper primary antibodies which were purchased from Cell Signaling Technology or Santa Cruz Biotechnology and secondary antibodies before visualization by chemiluminescence Kit (Millipore, USA).

Preparation of α,β,γ,δ-unsaturated pyrazolones 1

The solution of phenylhydrazine (324.4 mg, 3.0 mmol) with ethyl acetoacetate (468.5 mg, 3.6 mmol, 1.2 equiv) in acetic acid (2.0 mL) was refluxed for 8 h in oil bath, and left to cool. The pure product could be obtained by recrystallization by using acetic acid as a yellow solid, which could be used directly in next step without further purification. To a solution of the above product (348.4 mg, 2.0 mmol) in THF (5.0 mL) under argon atmosphere was added ethyl (*E*)-4-oxo-4-phenylbut-2-enoate (408.5 mg, 2.0 mmol, 1.0 equiv) and pyridine (474.6 mg, 6.0 mmol, 3.0 equiv). The mixture was stirred at -10 °C followed by addition of Titanium isopropoxide (1.42 g, 5.0 mmol, 2.5 equiv). The solution was stirred at room temperature until the reaction had stopped progressing as observed by TLC analysis, then diluted with EtOAc and washed with 1N aqueous HCl, Na_2CO_3, and brine. The organic layer was dried over Na_2SO_4, removed under reduced pressure, and purified by column chromatography (*n*-hexane/ethyl acetate = 20:1 to 15:1) to provide **1a**. Other α,β,γ,δ-unsaturated pyrazolones **1** were prepared according to the same procedure.

Ethyl-(2*E*,4*E*)-4-(3-methyl-5-oxo-1-phenyl-1,5-dihydro-4*H*-pyrazol-4-ylidene)-4-phenylbut-2-enoate (1a): red solid (*n*-hexane/ethyl acetate = 20:1 for purification), 583.8 mg, 54% yield, *E*/*Z* >20:1, m.p. 118–119 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 9.39 (d, *J* = 1 Hz, 1H), 7.92 (d, *J* = 9.0 Hz, 2H), 7.53 – 7.47 (m, 3H), 7.43 – 7.40 (m, 2H), 7.23 – 7.19 (m, 3H), 5.90 (d, *J* = 15.6 Hz, 1H), 4.25 (q, *J* = 7.2 Hz, 2H), 1.49 (s, 3H), 1.33 – 1.29 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ (ppm) 165.8, 162.7, 154.7, 148.9, 140.0, 138.0, 134.8, 134.6, 129.8, 128.9, 128.9, 128.7, 127.6, 125.2, 119.1, 61.3, 17.0, 14.3; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{22}H_{20}N_2O_3Na$ 383.1372; found 383.1370.

Ethyl-(2*E*,4*E*)-4-(4-fluorophenyl)-4-(3-methyl-5-oxo-1-phenyl-1,5-dihydro-4*H*-pyrazol-4-ylidene)but-2-enoate (1b): red solid (*n*-hexane/ethyl acetate = 18:1 for purification), 578.9 mg, 51% yield, *E*/*Z* >20:1, m.p. 153–154 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 9.36 (d, *J* = 15.8 Hz, 1H), 7.93 – 7.90 (m, 2H), 7.43 – 7.40 (m, 2H), 7.23 – 7.21 (m, 3H), 7.21 – 7.19 (m, 2H), 5.87 (d, *J* = 15.6 Hz, 1H), 4.25 (q, *J* = 7.2 Hz, 2H), 1.53 (s, 3H), 1.31 (t, *J* = 7.2 Hz, 3H);

$^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ (ppm) 165.6, 163.5 (d, J_{CF} = 249.3 Hz), 162.5, 153.3, 148.4, 140.0, 137.8, 134.4, 130.91 (d, J_{CF} = 8.6 Hz), 130.67 (d, J_{CF} = 3.5 Hz), 128.9, 127.9, 125.2, 119.0, 116.1, 115.9, 61.2, 17.1, 14.2; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for calcd for $C_{22}H_{19}FN_2O_3Na$ 401.1277; found 401.1275.

Ethyl-(2*E*,4*E*)-4-(3-bromophenyl)-4-(3-methyl-5-oxo-1-phenyl-1,5-dihydro-4*H*-pyrazol-4-ylidene)but-2-enoate (1c): red solid (*n*-hexane/ethyl acetate = 18:1 for purification), 777.6 mg, 59% yield, *E*/*Z* >20:1, m.p. 132–133 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 9.36 (d, *J* = 15.6 Hz, 1H), 7.92 – 7.90 (m, 2H), 7.66 (ddd, *J* = 8.4, 2.4, 1.2 Hz, 1H), 7.43 – 7.40 (m, 3H), 7.38 (t, *J* = 7.8 Hz, 1H), 7.22 – 7.19 (m, 1H), 7.19 – 7.17 (m, 1H), 5.88 (d, *J* = 15.6 Hz, 1H), 4.26 (q, *J* = 7.2 Hz, 2H), 1.54 (s, 3H), 1.32 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ (ppm) 165.5, 162.4, 152.2, 148.3, 139.4, 137.8, 136.6, 134.5, 132.8, 131.6, 130.3, 128.9, 127.8, 127.5, 125.2, 122.8, 119.0, 61.3, 17.1, 14.2; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{22}H_{19}BrN_2O_3Na$ 461.0477; found 461.0475.

Ethyl-(2*E*,4*E*)-4-(4-bromophenyl)-4-(3-methyl-5-oxo-1-phenyl-1,5-dihydro-4*H*-pyrazol-4-ylidene)but-2-enoate (1d): red solid (*n*-hexane/ethyl acetate = 18:1 for purification), 764.4 mg, 58% yield, *E*/*Z* >20:1, m.p. 137–138 °C, *n*-hexane/ethyl acetate = 18:1; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 9.35 (d, *J* = 15.6 Hz, 1H), 7.91 (dd, *J* = 9.0, 1.2 Hz, 2H), 7.66 – 7.64 (m, 2H), 7.41 (dd, *J* = 8.4, 7.8 Hz, 2H), 7.20 (tt, *J* = 8.0, 1.2 Hz, 1H), 7.13 – 7.11 (m, 2H), 5.86 (d, *J* = 15.6 Hz, 1H), 4.25 (q, *J* = 7.2 Hz, 2H), 1.54 (s, 3H), 1.31 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ (ppm) 165.5, 162.4, 152.9, 148.3, 139.6, 137.8, 134.4, 133.6, 132.0, 130.5, 128.99, 127.7, 125.2, 124.2, 119.0, 61.3, 17.2, 14.2; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{22}H_{19}BrN_2O_3Na$ 461.0477; found 461.0480.

Ethyl-(2*E*,4*E*)-4-(3,4-dichlorophenyl)-4-(3-methyl-5-oxo-1-phenyl-1,5-dihydro-4H-pyrazol-4-ylidene)but-2-enoate (1e): red solid (*n*-hexane/ethyl acetate = 18:1 for purification), 618.2 mg, 48% yield, *E*/*Z* >20:1, m.p. 170–171 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 9.33 (d, *J* = 15.6 Hz, 1H), 7.90 (dd, *J* = 8.4, 0.6 Hz, 2H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.41 (t, *J* = 7.8

Hz, 2H), 7.36 (d, *J* = 1.8 Hz, 1H), 7.22 – 7.19 (m, 1H), 7.10 (dd, *J* = 7.8, 1.8 Hz, 1H), 5.86 (d, *J* = 16.2 Hz, 1H), 4.25 (q, *J* = 7.2 Hz, 2H), 1.57 (s, 3H), 1.31 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ (ppm) 165.3, 162.2, 151.0, 147.9, 139.2, 137.7, 134.4, 134.4, 133.4, 130.9, 130.7, 128.9, 128.2, 127.9, 125.3, 118.9, 61.3, 17.3, 14.2; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{22}H_{18}Cl_2N_2O_3Na$ 451.0592; found 451.0595.

Ethyl-(2*E*,4*E*)-4-(3-methyl-5-oxo-1-phenyl-1,5-dihydro-4*H*-pyrazol-4-ylidene)-4-(o-tolyl)but-2-enoate (1f): red solid (*n*-hexane/ethyl acetate = 18:1 for purification), 730.2 mg, 65% yield, *E*/*Z* >20:1, m.p. 110–111 °C; ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 9.44 (d, *J* = 15.6 Hz, 1H), 7.93 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.43 – 7.37 (m, 3H), 7.31 (d, *J* = 7.8 Hz, 2H), 7.22 – 7.18 (m, 1H), 7.06 (d, *J* = 7.8 Hz, 1H), 5.85 (d, *J* = 15.6 Hz, 1H), 4.25 (q, *J* = 7.2 Hz, 2H), 2.17 (s, 3H), 1.43 (s, 3H), 1.31 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ (ppm) 165.7, 162.6, 154.4, 148.9, 138.9, 137.9, 135.3, 134.2, 133.6, 130.6, 129.6, 128.8, 128.5, 127.7, 126.1, 125.1, 118.9, 61.2, 19.5, 16.1, 14.2; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{23}H_{22}N_2O_3Na$ 397.1528; found 397.1525.

Ethyl-(2*E*,4*E*)-4-(3-methoxyphenyl)-4-(3-methyl-5-oxo-1-phenyl-1,5-dihydro-4*H*-pyrazol-4-ylidene)but-2-enoate (1g): red solid (*n*-hexane/ethyl acetate = 15:1 for purification), 702.8 mg, 60% yield, *E*/*Z* >20:1, m.p. 125–126 °C; ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 9.37 (d, *J* = 15.6 Hz, 1H), 7.93 – 7.92 (m, 2H), 7.42 – 7.38 (m, 3H), 7.21 – 7.18 (m, 1H), 7.03 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.80 (d, *J* = 7.2 Hz, 1H), 6.75 (d, *J* = 1.8 Hz, 1H), 5.95 (d, *J* = 15.6 Hz, 1H), 4.25 (q, *J* = 7.2 Hz, 2H), 3.85 (s, 3H), 1.56 (s, 3H), 1.31 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ (ppm) 165.7, 162.7, 159.6, 154.3, 148.8, 139.7, 137.9, 135.9, 134.4, 129.8, 128.8, 127.4, 125.1, 121.1, 118.9, 114.9, 114.5, 61.2, 55.4, 16.7, 14.2; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{23}H_{22}N_2O_4Na$ 413.1477; found 413.1476.

Ethyl-(2*E*,4*E*)-4-(4-methoxyphenyl)-4-(3-methyl-5-oxo-1-phenyl-1,5-dihydro-4*H*-pyrazol-4-ylidene)but-2-enoate (1h): red solid (*n*-hexane/ethyl acetate = 15:1 for purification),

726.2 mg, 62% yield, *E*/*Z* >20:1, m.p. 126–127 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 9.29 (d, *J* = 15.6 Hz, 1H), 7.93 (dd, *J* = 8.4, 0.6 Hz, 2H), 7.41 (dd, *J* = 8.4, 7.2 Hz, 2H), 7.19 (t, *J* = 7.2 Hz, 1H), 7.15 (d, *J* = 8.4 Hz, 2H), 7.00 (d, *J* = 9.0 Hz, 2H), 5.95 (d, *J* = 15.6 Hz, 1H), 4.25 (t, *J* = 7.2 Hz, 2H), 3.89 (s, 3H), 1.57 (s, 3H), 1.31 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ (ppm) 165.8, 162.8, 160.9, 154.8, 148.9, 140.7, 138.0, 134.3, 130.8, 128.8, 127.5, 127.0, 125.0, 119.0, 114.1, 61.1, 55.4, 17.1, 14.2; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{23}H_{22}N_2O_4Na$ 413.1477, found 413.1474.

Ethyl-(2E,4E)-4-(3-methyl-5-oxo-1-phenyl-1,5-dihydro-4H-pyrazol-4-ylidene)-4-(thiophen-2-yl)but-2-enoate (1i): red solid (*n*-hexane/ethyl acetate = 15:1 for purification), 714.5 mg, 65% yield, *E*/*Z* = 15:1, m.p. 120–121 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 9.23 (d, *J* = 15.6 Hz, 1H), 7.92 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.59 (dd, *J* = 4.8, 1.2 Hz, 1H), 7.41 (dd, *J* = 8.4, 7.8 Hz, 2H), 7.20 (t, *J* = 7.2 Hz, 1H), 7.17 (dd, *J* = 5.4, 4.8 Hz, 1H), 7.10 (dd, *J* = 3.0, 1.2 Hz, 1H), 6.15 (d, *J* = 15.6 Hz, 1H), 4.26 (t, *J* = 7.2 Hz, 2H), 1.72 (s, 3H), 1.32 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ (ppm) 165.6, 162.2, 148.5, 147.2, 140.6, 137.8, 134.4, 134.2, 130.7, 129.3, 129.1, 128.8, 127.5, 125.1, 119.0, 61.2, 16.2, 14.2; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{20}H_{18}SN_2O_3Na$ 389.0936; found 389.0939.

Ethyl-(2*E*,4*E*)-4-(3-methyl-5-oxo-1-phenyl-1,5-dihydro-4*H*-pyrazol-4-ylidene)-4-(naphthalen-2-yl)but-2-enoate (1j): red solid (*n*-hexane/ethyl acetate = 20:1 for purification), 615.7 mg, 50% yield, *E*/*Z* = 13:1, m.p. 156–157 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 9.44 (d, *J* = 15.6 Hz, 1H), 7.97 (d, *J* = 8.4 Hz, 1H), 7.95 – 7.93 (m, 3H), 7.90 – 7.88 (m, 1H), 7.72 (s, 1H), 7.62 – 7.60 (m, 2H), 7.42 (dd, *J* = 8.4, 7.8 Hz, 2H), 7.32 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.20 (t, *J* = 7.2 Hz, 1H), 5.90 (d, *J* = 15.6 Hz, 1H), 4.23 (q, *J* = 7.2 Hz, 2H), 1.45 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ (ppm) 165.6, 162.6, 154.5, 148.8, 140.0, 137.9, 134.6, 133.4, 132.5, 132.1, 128.8, 128.6, 128.5, 128.2, 127.9, 127.8, 127.4, 127.2, 126.0, 125.0, 118.9, 61.1, 17.1, 14.2; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{26}H_{22}N_2O_3Na$ 433.1528; found 433.1530.

Ethyl-(2*E*,4*E*)-4-(1-(2-fluorophenyl)-3-methyl-5-oxo-1,5-dihydro-4*H*-pyrazol-4-ylidene)-4-phenylbut-2-enoate (1k): red solid (*n*-hexane/ethyl acetate = 18:1 for purification), 647.1 mg, 57% yield, *E*/*Z* = 18:1, m.p. 104–105 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 9.36 (d, *J* = 15.6 Hz, 1H), 7.52 – 7.49 (m, 3H), 7.47 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.36 – 7.32 (m, 1H), 7.25 – 7.21 (m, 4H), 5.90 (d, *J* = 15.6 Hz, 1H), 4.23 (q, *J* = 7.2 Hz, 2H), 1.48 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ (ppm) 165.7, 163.0, 156.70 (d, J_{CF} = 251.3 Hz), 155.1, 149.3, 139.8, 134.7, 134.6, 129.7, 129.31 (d, J_{CF} = 7.8 Hz), 128.7, 128.6, 127.2, 126.4, 124.74 (d, J_{CF} = 11.9 Hz), 124.41 (d, J_{CF} = 3.8 Hz), 116.9, 116.8, 61.2, 16.9, 14.2; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{22}H_{19}FN_2O_3Na$ 401.1277; found 401.1275.

Ethyl-(2*E*,4*E*)-4-(1-(3-chlorophenyl)-3-methyl-5-oxo-1,5-dihydro-4*H*-pyrazol-4-ylidene)-4-phenylbut-2-enoate (1l): red solid (*n*-hexane/ethyl acetate = 18:1 for purification), 651.5 mg, 55% yield, *E*/*Z* = 15:1, m.p. 105–106 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 9.35 (d, *J* = 15.6 Hz, 1H), 8.01 (t, *J* = 2.4 Hz, 1H), 7.90 (ddd, *J* = 8.4, 1.8, 0.6 Hz, 1H), 7.53 – 7.51 (m, 2H), 7.50 – 7.48 (m, 1H), 7.33 (t, *J* = 8.4 Hz, 1H), 7.22 (dd, *J* = 7.2, 1.2 Hz, 2H), 7.16 (ddd, *J* = 7.8, 1.8, 0.8 Hz, 1H), 5.91 (d, *J* = 15.6 Hz, 1H), 4.26 (q, *J* = 7.2 Hz, 2H), 1.49 (s, 3H), 1.31 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ (ppm) 165.6, 162.7, 155.1, 149.3, 139.8, 138.9, 134.8, 134.6, 129.9, 129.8, 128.8, 128.7, 127.2, 124.9, 118.6, 116.5, 61.2, 16.9, 14.2; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{22}H_{19}ClN_2O_3Na$ 417.0982; found 417.0980.

Ethyl-(2*E*,4*E*)-4-(3-methyl-5-oxo-1-(p-tolyl)-1,5-dihydro-4*H*-pyrazol-4-ylidene)-4-phenylbut-2-enoate (1m): red solid (*n*-hexane/ethyl acetate = 18:1 for purification), 685.2 mg, 61% yield, *E*/*Z* = 18:1, m.p. 107–108 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 9.39 (d, *J* = 15.6 Hz, 1H), 7.79 (d, *J* = 8.4 Hz, 2H), 7.51 – 7.47 (m, 3H), 7.22 – 7.20 (m, 4H), 5.89 (d, *J* = 15.6 Hz, 1H), 4.25 (q, *J* = 7.2 Hz, 2H), 2.35 (s, 3H), 1.48 (s, 3H), 1.31 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ (ppm) 165.7, 162.5, 154.4, 148.6, 140.0, 135.5, 134.8, 134.4, 129.6,

129.4, 128.8, 128.6, 127.6, 119.0, 61.1, 21.0, 16.8, 14.2; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{23}H_{22}N_2O_3Na$ 397.1528; found 397.1525

Ethyl-(2*E*,4*E*)-4-(5-oxo-1,3-diphenyl-1,5-dihydro-4*H*-pyrazol-4-ylidene)-4-phenylbut-2-enoate (1n): red solid (*n*-hexane/ethyl acetate = 18:1 for purification), 646.4 mg, 51% yield, *E*/*Z* = 15:1, m.p. 166–167 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 9.41 (d, *J* = 15.6 Hz, 1H), 8.02 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.43 (dd, *J* = 8.4, 7.2 Hz, 2H), 7.24 – 7.21 (m, 1H), 7.14 – 7.11 (m, 1H), 7.08 – 7.05 (m, 1H), 7.02 – 7.00 (m, 2H), 6.98 – 6.96 (m, 4H), 6.95 – 6.93 (m, 2H), 6.03 (d, *J* = 15.6 Hz, 1H), 4.27 (q, *J* = 7.2 Hz, 2H), 1.32 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ (ppm) 165.7, 163.1, 156.0, 151.3, 140.7, 138.0, 134.8, 134.2, 132.2, 130.7, 129.9, 128.8, 128.0, 127.9, 127.7, 127.6, 125.5, 125.3, 119.3, 61.2, 14.2; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{27}H_{22}N_2O_3Na$ 445.1528; found 445.1525.

(*E*)-4-((*E*)-1,3-diphenylallylidene)-5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (1o): red solid (*n*-hexane/ethyl acetate = 18:1 for purification), 688.7 mg, 63% yield, *E*/*Z* = 18:1, m.p. 160–161 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 9.32 (d, *J* = 15.6 Hz, 1H), 7.97 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.58 – 7.56 (m, 2H), 7.53 – 7.49 (m, 3H), 7.41 (dd, *J* = 8.4, 7.2 Hz, 2H), 7.35 – 7.33 (m, 3H), 7.29 – 7.28 (m, 2H), 7.20 – 7.17 (m, 1H), 6.70 (d, *J* = 15.6 Hz, 1H), 1.47 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ (ppm) 163.7, 158.7, 149.2, 147.9, 138.3, 136.0, 135.9, 130.4, 129.2, 129.0, 128.9, 128.8, 128.6, 128.4, 126.7, 124.8, 123.3, 119.1, 16.8; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{25}H_{20}N_2ONa$ 387.1473; found 387.1470.

Procedure for the asymmetric synthesis of 3 and 4 (including some diastereoisomers of 4')

To α,β,γ,δ-unsaturated pyrazolone **1** (0.15 mmol), amine catalyst **Cat. III** (20 mol%), benzoic acid (30 mol%), and THF/H_2O (20:1 in v/v, 1.5 mL) in a standard glass vial with stir bar was added aldehyde **2** (0.30 mmol). The reaction mixture was stirred at reaction temperature of -20

°C until the reaction completed (monitored by TLC). The reaction mixture was concentrated and the residue was purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate = 4:1) to give the spirocyclohexene-pyrazolone derivate **3**. To a solution of spirocyclohexene-pyrazolone derivate **3** in CH_2Cl_2 (1.0 mL) was added TEA (0.3 mmol in 0.5 mL CH_2Cl_2) at ice bath, after which TMSCl (0.2 mmol in 0.5 mL CH_2Cl_2) was added. The reaction mixture was stirred until the reaction completed (monitored by TLC). Then the reaction was quenched with aqueous $NaHCO_3$, extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by chromatography on silica gel (*n*-hexane/ethyl acetate = 20:1) to give the TMS-protected spirocyclohexene-pyrazolone derivate **4** which was dried under vacuum and further analysed by ^{1}H-NMR, ^{13}C{^{1}H}-NMR, HRMS, chiral HPLC analysis, *etc*. The diastereoisomers of **4'** were synthesized and analysed according to the same procedure.

Ethyl-(5*S*,8*R*,9*R*,10*S*)-10-hydroxy-1,9-dimethyl-4-oxo-3,6-diphenyl-2,3-diazaspiro[4.5]-deca-1,6-diene-8-carboxylate (3a): white solid, 53.4 mg, 85% yield, dr 84:16, m.p. 189-190 °C; $[\alpha]_D^{20}$ = +26.9 (*c* = 0.21 in CH_2Cl_2); ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm) 7.82 (d, *J* = 7.2 Hz, 2H), 7.44 (t, *J* = 7.8 Hz, 2H), 7.26 – 7.25 (m, 3H), 7.20 (t, *J* = 7.2 Hz, 1H), 6.98 (dd, *J* = 6.6, 3.0 Hz, 2H), 6.12 (d, *J* = 4.8 Hz, 1H), 5.66 (d, *J* = 6.6 Hz, 1H), 4.30 (dd, *J* = 10.8, 6.0 Hz, 1H), 4.21 – 4.14 (m, 2H), 3.57 (t, *J* = 6.0 Hz, 1H), 2.90 – 2.83 (m, 1H), 1.80 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.00 (d, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6) δ (ppm) 172.9, 172.1, 162.1, 139.5, 138.5, 136.2, 130.0, 129.5, 129.1, 128.6, 126.6, 125.2, 118.7, 69.8, 66.0, 61.1, 48.2, 29.5, 14.7, 14.6, 14.3; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{25}H_{26}N_2O_4Na$ 441.1790; found 441.1792.

Ethyl-(5*S*,8*R*,9*R*,10*S*)-1,9-dimethyl-4-oxo-3,6-diphenyl-10-((trimethylsilyl)oxy)-2,3-di-azaspiro[4.5]deca-1,6-diene-8-carboxylate (4a): oil, 55.2 mg, 75% yield, dr 84:16, *ee* 97%, $[\alpha]_D^{20}$ = +16.2 (*c* = 0.12 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.94 (d, *J* = 7.6 Hz, 2H), 7.41 (t, *J* = 8.0 Hz, 2H), 7.23 – 7.18 (m, 4H), 7.04 (dd, *J* = 6.8, 2.4 Hz, 2H), 6.15 (d, *J* = 2.4 Hz, 1H), 4.27 – 4.17 (m, 2H), 3.85 (d, *J* = 10.4 Hz, 1H), 3.28 – 3.21 (m, 1H), 3.05 (dd, *J* =

10.4, 2.4 Hz, 1H), 1.78 (s, 3H), 1.29 (t, J = 7.2 Hz, 3H), 1.09 (d, J = 6.4 Hz, 3H), 0.05 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 172.1, 171.9, 160.3, 139.0, 138.3, 134.8, 130.0, 128.8, 128.7, 128.1, 126.3, 124.8, 118.9, 65.5, 61.2, 50.7, 30.5, 29.7, 16.9, 14.7, 14.2, 0.8; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{28}H_{34}N_2O_4SiNa$ 513.2186; found 513.2189.

Ethyl-(5*S*,8*R*,9*R*,10*S*)-6-(4-fluorophenyl)-10-hydroxy-1,9-dimethyl-4-oxo-3-phenyl-2,3-diazaspiro[4.5]deca-1,6-diene-8-carboxylate (3b): white solid, 57.6 mg, 88% yield, dr 85:15, m.p. 167-168 °C; $[\alpha]_D^{20}$ = +18.2 (*c* = 0.11 in CH_2Cl_2); ^1H NMR (600 MHz, DMSO-d_6) δ (ppm) 7.81 (d, J = 8.4 Hz, 2H), 7.44 (t, J = 7.8 Hz, 2H), 7.21 (t, J = 7.8 Hz, 1H), 7.11 (t, J = 9.0 Hz, 2H), 7.01 (dd, J = 8.4, 5.4 Hz, 2H), 6.12 (d, J = 4.8 Hz, 1H), 5.67 (d, J = 6.0 Hz, 1H), 4.29 (dd, J = 11.4, 6.6 Hz, 1H), 4.21 – 4.14 (m, 2H), 3.57 (t, J = 5.4 Hz, 1H), 2.87 – 2.81 (m, 1H), 1.82 (s, 3H), 1.26 (t, J = 7.2 Hz, 3H), 0.99 (d, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, DMSO-d_6) δ (ppm) 172.8, 172.0, 162.2 (d, J_{CF} = 243.6 Hz), 162.0, 138.4, 135.8 (d, J_{CF} = 3.5 Hz), 135.1, 130.4, 129.5, 128.7 (d, J_{CF} = 8.6 Hz), 125.3, 118.8, 116.1 (d, J_{CF} = 21.5 Hz), 69.8, 66.1, 61.1, 48.1, 29.6, 14.7, 14.6, 14.3; ^{19}F NMR (565 MHz, DMSO-d_6) δ (ppm) -113.82; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{25}H_{25}FN_2O_4Na$ 459.1696; found 459.1693.

Ethyl-(5*S*,8*R*,9*R*,10*S*)-6-(4-fluorophenyl)-1,9-dimethyl-4-oxo-3-phenyl-10-((trimethylsilyl)oxy)-2,3-diazaspiro[4.5]deca-1,6-diene-8-carboxylate (4b): oil, 62.6 mg, 82% yield, dr 85:15, *ee* 93%, $[\alpha]_D^{20}$ = +10.2 (*c* = 0.09 in CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.90 – 7.88 (m, 2H), 7.43 – 7.39 (m, 2H), 7.20 (t, J = 7.6 Hz, 1H), 7.04 (dd, J = 8.8, 5.2 Hz, 2H), 6.89 (t, J = 8.8 Hz, 2H), 6.11 (d, J = 5.6 Hz, 1H), 4.64 (d, J = 11.2 Hz, 1H), 4.27 – 4.20 (m, 2H), 3.56 (t, J = 5.6 Hz, 1H), 3.10 – 3.01 (m, 1H), 1.89 (s, 3H), 1.35 (t, J = 7.2 Hz, 3H), 1.06 (d, J = 6.8 Hz, 3H), 0.03 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 172.1, 171.8, 162.1 (d, J_{CF} = 246.1 Hz), 160.4, 137.6, 135.2, 134.6 (d, J_{CF} = 3.4 Hz), 129.2, 128.4, 127.9 (d, J_{CF} = 8.1 Hz), 124.6, 118.6, 115.1 (d, J_{CF} = 21.4 Hz), 72.2, 65.8, 60.6, 47.9, 29.8, 24.9, 14.6, 14.0, 13.9, 0.3; ^{19}F NMR (565 MHz, DMSO-d_6) δ (ppm) -113.58; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{28}H_{33}FN_2O_4SiNa$ 531.2091; found 531.2093.

Ethyl-(5*S*,8*R*,9*R*,10*S*)-6-(3-bromophenyl)-10-hydroxy-1,9-dimethyl-4-oxo-3-phenyl-2,3-diazaspiro[4.5]deca-1,6-diene-8-carboxylate (3c): white solid, 67.2 mg, 90% yield, dr 82:18, m.p. 156-157 °C; $[\alpha]_D^{20}$ = +20.6 (*c* = 0.16 in CH_2Cl_2); ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm) 7.78 (d, *J* = 7.8 Hz, 2H), 7.47 – 7.43 (m, 3H), 7.25 – 7.20 (m, 2H), 7.13 (s, 1H), 6.99 (d, *J* = 7.8 Hz, 1H), 6.22 (d, *J* = 5.4 Hz, 1H), 5.64 (d, *J* = 5.4 Hz, 1H), 4.29 (dd, *J* = 11.4, 6.6 Hz, 1H), 4.21 – 4.14 (m, 2H), 3.58 (t, *J* = 6.0 Hz, 1H), 2.87 – 2.83 (m, 1H), 1.83 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.00 (d, *J* = 6.6 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6) δ (ppm) 172.7, 171.8, 161.8, 141.6, 138.3, 134.7, 131.4, 131.3, 129.5, 129.3, 125.8, 125.5, 122.3, 119.1, 69.8, 65.9, 61.1, 48.2, 29.6, 14.7, 14.6, 14.3; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{25}H_{25}BrN_2O_4Na$ 519.0895; found 519.0897.

Ethyl-(5*S*,8*R*,9*R*,10*S*)-6-(3-bromophenyl)-1,9-dimethyl-4-oxo-3-phenyl-10-((trimethylsilyl)oxy)-2,3-diazaspiro[4.5]deca-1,6-diene-8-carboxylate (4c): oil, 71.8 mg, 84% yield, dr 82:18, *ee* 97%, $[\alpha]_D^{20}$ = +9.6 (*c* = 0.13 in CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.89 (d, *J* = 7.8 Hz, 2H), 7.41 (t, *J* = 7.8 Hz, 2H), 7 .21 – 7.14 (m, 2H), 6.95 – 6.91 (m, 1H), 6.83 – 6.80 (m, 2H), 6.16 (d, *J* = 5.4 Hz, 1H), 4.64 (d, *J* = 10.8 Hz, 1H), 4.27 – 4.21 (m, 2H), 3.57 (t, *J* = 5.4 Hz, 1H), 3.10 – 3.04 (m, 1H), 1.89 (s, 3H), 1.35 (t, *J* = 7.2 Hz, 3H), 1.06 (d, *J* = 6.6 Hz, 3H), 0.03 (s, 9H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ (ppm) 172.5, 172.2, 160.7, 141.0, 138.0, 135.4, 131.3, 130.5, 130.3, 130.1, 128.9, 125.3, 124.9, 122.7, 119.4, 72.7, 66.0, 61.2, 48.4, 30.3, 15.1, 14.6, 14.5, 0.8, 0.6; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{28}H_{33}BrN_2O_4Si^+Na$ 591.1291; found 591.1294.

Ethyl-(5*S*,8*R*,9*R*,10*S*)-6-(4-bromophenyl)-10-hydroxy-1,9-dimethyl-4-oxo-3-phenyl-2,3-diazaspiro[4.5]deca-1,6-diene-8-carboxylate (3d): white solid, 67.9 mg, 91% yield, dr 82:18, m.p. 162-163 °C; $[\alpha]_D^{20}$ = +19.8 (*c* = 0.15 in CH_2Cl_2); ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm) 7.81 – 7.79 (m, 2H), 7.49 – 7.47 (m, 2H), 7.45 – 7.43 (m, 2H), 7.21 (t, *J* = 7.8 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 2H), 6.16 (d, *J* = 4.8 Hz, 1H), 5.67 (d, *J* = 6.0 Hz, 1H), 4.28 (dd, *J* = 11.4, 6.0 Hz, 1H), 4.21 – 4.14 (m, 2H), 3.57 (t, *J* = 5.4 Hz, 1H), 2.87 – 2.80 (m, 1H), 1.82 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H), 0.99 (d, *J* = 6.6 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6) δ (ppm) 172.7,

171.9, 161.9, 138.6, 138.4, 135.0, 132.1, 130.8, 129.5, 128.8, 125.3, 121.9, 118.9, 69.8, 65.9, 61.1, 48.1, 29.5, 14.7, 14.6, 14.3; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{25}H_{25}BrN_2O_4Na$ 519.0895; found 519.0898.

Ethyl-(5*S*,8*R*,9*R*,10*S*)-6-(4-bromophenyl)-1,9-dimethyl-4-oxo-3-phenyl-10-((trimethylsilyl)oxy)-2,3-diazaspiro[4.5]deca-1,6-diene-8-carboxylate (4d): oil, 70.1 mg, 82% yield, dr 82:18, *ee* 97%, $[\alpha]_D^{20}$ = +53.4 (*c* = 0.18 in CH_2Cl_2); ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.89 (d, *J* = 7.8 Hz, 2H), 7.41 (t, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.20 (t, *J* = 7.2 Hz, 1H), 6.93 (d, *J* = 9.0 Hz, 2H), 6.13 (d, *J* = 5.4 Hz, 1H), 4.63 (d, *J* = 10.8 Hz, 1H), 4.27 – 4.20 (m, 2H), 3.56 (t, *J* = 5.4 Hz, 1H), 3.10 – 3.03 (m, 1H), 1.88 (s, 3H), 1.35 (t, *J* = 7.2 Hz, 3H), 1.06 (d, *J* = 6.6 Hz, 3H), 0.03 (s, 9H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ (ppm) 172.4, 172.1, 160.6, 137.9, 137.8, 135.5, 131.7, 129.9, 128.8, 128.2, 125.0, 122.3, 118.9, 72.6, 66.0, 61.0, 48.3, 30.2, 15.0, 14.4, 14.3, 0.6; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{28}H_{33}BrN_2O_4SiNa$ 591.1291; found 591.1290.

Ethyl-(5*S*,8*R*,9*R*,10*S*)-6-(3,4-dichlorophenyl)-10-hydroxy-1,9-dimethyl-4-oxo-3-phenyl-2,3-diazaspiro[4.5]deca-1,6-diene-8-carboxylate (3e): white solid, 58.5 mg, 80% yield, dr 80:20, m.p. 166-167 °C; $[\alpha]_D^{20}$ = +6.3 (*c* = 0.22 in CH_2Cl_2); ^1H NMR (600 MHz, DMSO-d_6) δ 7.79 (dd, *J* = 9.0, 1.2 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.47 – 7.44 (m, 2H), 7.22 (dt, *J* = 7.2, 1.2 Hz, 1H), 7.16 (d, *J* = 1.8 Hz, 1H), 6.96 (dd, *J* = 8.4, 1.2 Hz, 1H), 6.30 (d, *J* = 5.4 Hz, 1H), 5.75 (d, *J* = 6.6 Hz, 1H), 4.28 (dd, *J* = 11.4, 6.6 Hz, 1H), 4.19 – 4.14 (m, 2H), 3.61 – 3.59 (m, 1H), 2.84 – 2.80 (m, 1H), 1.84 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H), 0.99 (d, *J* = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, DMSO-d_6) δ (ppm) 172.6, 171.7, 161.9, 139.8, 138.2, 133.6, 132.0, 131.8, 131.5, 131.4, 131.2, 129.5, 128.4, 126.9, 125.5, 119.0, 69.7, 65.7, 61.2, 48.1, 29.5, 14.7, 14.6, 14.3; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{25}H_{24}Cl_2N_2O_4Na$ 509.1011; found 509.1014.

Ethyl-(5*S*,8*R*,9*R*,10*S*)-6-(3,4-dichlorophenyl)-1,9-dimethyl-4-oxo-3-phenyl-10-((trimethyl

silyl)oxy)-2,3-diazaspiro[4.5]deca-1,6-diene-8-carboxylate (4e): oil, 60.4 mg, 72% yield, dr 80:20, *ee* 93%, $[\alpha]_D^{20}$ = -35.6 (*c* = 0.10 in CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.88 (d, *J* = 8.4 Hz, 2H), 7.44 (t, *J* = 7.8 Hz, 2H), 7.29 – 7.27 (m, 1H), 7.24 – 7.22 (m, 2H), 6.89 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.18 (d, *J* = 5.4 Hz, 1H), 4.65 (d, *J* = 11.4 Hz, 1H), 4.30 – 4.23 (m, 2H), 3.59 (t, *J* = 5.4 Hz, 1H), 3.12 – 3.04 (m, 1H), 1.93 (s, 3H), 1.37 (t, *J* = 7.2 Hz, 3H), 1.08 (d, *J* = 7.2 Hz, 3H), 0.05 (s, 9H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ (ppm) 172.2, 172.0, 160.4, 138.8, 137.8, 134.5, 132.7, 132.3, 130.8, 130.7, 130.6, 128.8, 125.5, 125.2, 119.2, 72.6, 65.9, 61.2, 48.3, 30.2, 15.0, 14.5, 14.4, 0.7; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{28}H_{32}Cl_2N_2O_4SiNa$ 581.1406; found 581.1408.

Ethyl-(5*S*,8*R*,9*R*,10*S*)-10-hydroxy-1,9-dimethyl-4-oxo-3-phenyl-6-(o-tolyl)-2,3-diaza-spiro[4.5]deca-1,6-diene-8-carboxylate (3f): white solid, 52.6 mg, 81% yield, dr 78:22, m.p. 173-174 °C; $[\alpha]_D^{20}$ = -17.3 (*c* = 1.05 in CH_2Cl_2); ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm) 7.48 (dd, *J* = 9.0, 1.2 Hz, 2H), 7.30 (dd, *J* = 8.4, 7.8 Hz, 2H), 7.14 (d, *J* = 7.8 Hz, 1H), 7.11 – 7.08 (m, 1H), 7.06 (td, *J* = 7.2, 1.2 Hz, 1H), 6.98 (t, *J* = 7.2 Hz, 1H), 6.80 (d, *J* = 7.8 Hz, 1H), 5.77 (d, *J* = 6.6 Hz, 1H), 5.75 (d, *J* = 3.0 Hz, 1H), 4.17 – 4.13 (m, 2H), 3.92 (dd, *J* = 11.4, 6.6 Hz, 1H), 3.30 (dd, *J* = 10.2, 3.0 Hz, 1H), 2.33 (s, 3H), 2.29 (s, 3H), 1.21 (t, *J* = 7.2 Hz, 2H), 1.10 (d, *J* = 6.6 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6) δ (ppm) 174.2, 172.8, 159.7, 138.0, 137.6, 136.7, 132.8, 130.9, 130.7, 129.3, 128.1, 127.4, 125.4, 125.2, 118.7, 74.8, 67.7, 61.3, 50.2, 33.7, 20.6, 17.4, 17.0, 14.6; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{26}H_{28}N_2O_4Na$ 455.1947; found 455.1945.

Ethyl-(5*S*,8*R*,9*R*,10*S*)-1,9-dimethyl-4-oxo-3-phenyl-6-(o-tolyl)-10-((trimethylsilyl)oxy)-2,3-diazaspiro[4.5]deca-1,6-diene-8-carboxylate (4f): oil, 56.0 mg, 74% yield, dr 78:22, *ee* 90%, $[\alpha]_D^{20}$ = -20.7 (*c* = 0.09 in CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.40 – 7.39 (m, 2H), 7.20 – 7.27 (m, 2H), 7.07 (d, *J* = 7.8 Hz, 1H), 7.00 – 6.98 (m, 2H), 6.89 (t, *J* = 7.8 Hz, 1H), 6.82 (d, *J* = 7.8 Hz, 1H), 5.71 (d, *J* = 2.4 Hz, 1H), 4.18 – 4.13 (m, 3H), 3.15 (dd, *J* = 10.2, 2.4 Hz, 1H), 2.54 – 2.50 (m, 1H), 2.37 (s, 3H), 2.30 (s, 3H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.08 (d, *J* = 6.6 Hz, 3H), -0.08 (s, 9H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ (ppm) 173.7, 172.7, 159.6,

137.6, 136.7, 136.6, 133.6, 130.6, 129.9, 128.6, 127.9, 127.6, 125.0, 124.9, 119.3, 76.5, 67.9, 61.3, 50.4, 33.9, 20.4, 17.4, 17.3, 14.3, 0.5; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{29}H_{36}N_2O_4SiNa$ 527.2342; found 527.2344.

Ethyl-(5*S*,8*R*,9*R*,10*S*)-10-hydroxy-6-(3-methoxyphenyl)-1,9-dimethyl-4-oxo-3-phenyl-2,3-diazaspiro[4.5]deca-1,6-diene-8-carboxylate (3g): white solid, 53.8 mg, 80% yield, dr 70:30, m.p. 76-77 °C; $[\alpha]_D^{20}$ = +20.3 (*c* = 0.07 in CH_2Cl_2); ^1H NMR (600 MHz, DMSO-d_6) δ 7.84 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.44 (dd, *J* = 8.4, 7.2 Hz, 2H), 7.22 – 7.17 (m, 2H), 6.83 – 6.82 (m, 1H), 6.60 (dd, *J* = 6.6, 0.6 Hz, 1H), 6.46 (t, *J* = 1.8 Hz, 1H), 6.15 (d, *J* = 5.4 Hz, 1H), 5.69 (d, *J* = 6.6 Hz, 1H), 4.29 (dd, *J* = 10.8, 6.6 Hz, 1H), 4.21 – 4.13 (m, 2H), 3.57 (dd, *J* = 5.4, 2.4 Hz, 1H), 3.52 (s, 3H), 2.88 – 2.82 (m, 1H), 1.82 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H), 0.99 (d, *J* = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, DMSO-d_6) δ 173.0, 172.1, 162.3, 159.5, 140.8, 138.5, 135.9, 130.3, 130.1, 129.5, 125.2, 119.1, 118.5, 114.2, 111.6, 69.8, 66.0, 61.1, 55.2, 48.1, 29.5, 14.7, 14.6, 14.3; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{26}H_{28}N_2O_5Na$ 471.1896; found 471.1894.

Ethyl-(5*S*,8*R*,9*R*,10*S*)-6-(3-methoxyphenyl)-1,9-dimethyl-4-oxo-3-phenyl-10-((trimethylsilyl)oxy)-2,3-diazaspiro[4.5]deca-1,6-diene-8-carboxylate (4g): oil, 55.4 mg, 71% yield, dr 70:30, *ee* 90%, $[\alpha]_D^{20}$ = -22.1 (*c* = 0.25 in CH_2Cl_2); ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.92 (dd, *J* = 9.0, 1.2 Hz, 2H), 7.41 – 7.38 (m, 2H), 7.18 (tt, *J* = 7.8, 1.2 Hz, 1H), 7.13 – 7.10 (m, 1H), 6.76 (ddd, *J* = 8.2, 2.4, 0.6 Hz, 1H), 6.67 – 6.66 (m, 1H), 6.60 – 6.58 (m, 1H), 6.16 (d, *J* = 5.4 Hz, 1H), 4.65 (d, *J* = 10.8 Hz, 1H), 4.26 – 4.22 (m, 2H), 3.56 (t, *J* = 5.4 Hz, 1H), 3.55 (s, 3H), 3.11 – 3.06 (m, 1H), 1.89 (s, 3H), 1.35 (t, *J* = 7.2 Hz, 3H), 1.06 (d, *J* = 6.6 Hz, 3H), 0.04 (s, 9H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ (ppm) 172.9, 172.4, 161.2, 159.6, 140.4, 138.3, 136.5, 129.7, 129.4, 128.9, 125.0, 119.2, 118.9, 114.4, 111.4, 72.8, 66.3, 61.1, 55.1, 48.5, 30.3, 15.1, 14.6, 14.5, 0.8; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{29}H_{36}N_2O_5SiNa$ 543.2291; found 543.2288.

Ethyl-6-(3-methoxyphenyl)-1,9-dimethyl-4-oxo-3-phenyl-10-((trimethylsilyl)oxy)-2,3-diazaspiro[4.5]deca-1,6-diene-8-carboxylate (4g'): oil, 14.1 mg, 18% yield, dr 30:70, *ee* 39%, $[\alpha]_D^{20}$ = -24.1 (*c* = 0.10 in CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.96 (dd, *J* = 9.0, 1.2 Hz, 2H), 7.40 (dd, *J* = 8.4, 7.2 Hz, 2H), 7.18 (tt, *J* = 7.2, 1.2 Hz, 1H), 7.12 (t, *J* = 7.8 Hz, 1H), 6.76 (ddd, *J* = 8.4, 2.4, 0.6 Hz, 1H), 6.66 – 6.64 (m, 1H), 6.57 (t, *J* = 2.4 Hz, 1H), 6.17 (d, *J* = 3.0 Hz, 1H), 4.26 – 4.18 (m, 2H), 3.85 (d, *J* = 10.8 Hz, 1H), 3.55 (s, 3H), 3.29 – 3.15 (m, 1H), 3.05 (dd, *J* = 10.2, 2.4 Hz, 1H), 1.81 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.08 (d, *J* = 6.6 Hz, 3H), 0.05 (s, 9H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ (ppm) 172.2, 171.9, 160.5, 159.5, 140.3, 138.2, 134.7, 129.9, 129.7, 128.8, 124.8, 118.8, 118.7, 114.4, 110.9, 76.7, 65.5, 61.3, 55.0, 50.6, 30.5, 16.9, 14.7, 14.2, 0.8; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{29}H_{36}N_2O_5SiNa$ 543.2291; found 543.2294.

Ethyl-(5*S*,8*R*,9*R*,10*S*)-10-hydroxy-6-(4-methoxyphenyl)-1,9-dimethyl-4-oxo-3-phenyl-2,3-diazaspiro[4.5]deca-1,6-diene-8-carboxylate (3h): white solid, 53.8 mg, 80% yield, dr 73:27, m.p. 83-84 °C; $[\alpha]_D^{20}$ = +30.3 (*c* = 0.22 in CH_2Cl_2); ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm) 7.82 (d, *J* = 7.2 Hz, 2H), 7.44 (t, *J* = 7.2 Hz, 2H), 7.20 (t, *J* = 7.2 Hz, 1H), 6.90 (d, *J* = 7.8 Hz, 2H), 6.81 (d, *J* = 9.0 Hz, 2H), 6.05 (d, *J* = 4.8 Hz, 1H), 5.62 (d, *J* = 5.4 Hz, 1H), 4.28 (dd, *J* = 10.8, 6.0 Hz, 1H), 4.19 – 4.14 (m, 2H), 3.68 (s, 3H), 3.56 – 3.53 (m, 1H), 2.85 – 2.81 (m, 1H), 1.80 (s, 3H), 1.26 (td, *J* = 7.2, 1.8 Hz, 3H), 0.98 (d, *J* = 6.0 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6) δ (ppm) 173.0, 172.2, 162.3, 159.5, 138.6, 135.7, 131.8, 129.5, 128.9, 127.7, 125.2, 118.7, 114.5, 69.8, 66.1, 61.0, 55.6, 48.1, 29.6, 14.7, 14.7, 14.3; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{26}H_{28}N_2O_5Na$ 471.1896; found 471.1893.

Ethyl-(5*S*,8*R*,9*R*,10*S*)-6-(4-methoxyphenyl)-1,9-dimethyl-4-oxo-3-phenyl-10-((trimethylsilyl)oxy)-2,3-diazaspiro[4.5]deca-1,6-diene-8-carboxylate (4h): oil, 57.0 mg, 73% yield, dr 73:27, *ee* 98%, $[\alpha]_D^{20}$ = +4.3 (*c* = 0.13 in CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.92 (d, *J* = 7.8 Hz, 2H), 7.41 (t, *J* = 8.4 Hz, 2H), 7.19 (t, *J* = 7.2 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 2H), 6.72 (d, *J* = 9.0 Hz, 2H), 6.08 (d, *J* = 5.4 Hz, 1H), 4.64 (d, *J* = 11.4 Hz, 1H), 4.26 – 4.20 (m, 2H), 3.73 (s, 3H), 3.55 (t, *J* = 5.4 Hz, 1H), 3.08 – 3.04 (m, 1H), 1.87 (s, 3H), 1.34 (t, *J* = 7.2

Hz, 3H), 1.05 (d, *J* = 6.6 Hz, 3H), 0.03 (s, 9H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ (ppm) 172.7, 172.4, 161.2, 159.3, 138.1, 136.0, 131.4, 128.7, 128.6, 128.4, 127.7, 124.8, 118.9, 113.8, 72.7, 66.2, 60.9, 55.1, 48.3, 30.2, 15.1, 14.4, 14.3, 0.7; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{29}H_{36}N_2O_5SiNa$ 543.2291; found 543.2290.

Ethyl-6-(4-methoxyphenyl)-1,9-dimethyl-4-oxo-3-phenyl-10-((trimethylsilyl)oxy)-2,3-diazaspiro[4.5]deca-1,6-diene-8-carboxylate (4h'): oil, 13.3 mg, 17% yield, dr 27:73, *ee* 12%, $[\alpha]_D^{20}$ = -26.5 (*c* = 0.11 in CH_2Cl_2); ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.95 (dd, *J* = 9.0, 1.2 Hz, 2H), 7.41 (dd, *J* = 8.4, 7.2 Hz, 2H), 7.19 (td, *J* = 7.8, 1.2 Hz, 1H), 6.97 (d, *J* = 9.0 Hz, 2H), 6.73 (d, *J* = 9.0 Hz, 2H), 6.09 (d, *J* = 3.0 Hz, 1H), 4.27 – 4.16 (m, 2H), 3.84 (d, *J* = 10.8 Hz, 1H), 3.74 (s, 3H), 3.25 – 3.18 (m, 1H), 3.03 (dd, *J* = 10.2, 2.4 Hz, 1H), 1.79 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.08 (d, *J* = 6.6 Hz, 3H), 0.05 (s, 9H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ (ppm) 172.2, 172.0, 164.7, 159.4, 138.3, 134.2, 131.4, 128.9, 128.8, 127.5, 124.8, 118.9, 113.9, 99.9, 76.7, 65.6, 61.2, 55.2, 50.7, 30.6, 16.8, 14.6, 14.2, 0.77; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{29}H_{36}N_2O_5SiNa$ 543.2291; found 543.2289.

Ethyl-(5*S*,8*R*,9*R*,10*S*)-10-hydroxy-1,9-dimethyl-4-oxo-3-phenyl-6-(thiophen-2-yl)-2,3-diazaspiro[4.5]deca-1,6-diene-8-carboxylate (3i): white solid, 55.4 mg, 87% yield, dr 83:17, m.p. 158-159 °C; $[\alpha]_D^{20}$ = +25.8 (*c* = 0.30 in CH_2Cl_2); ^1H NMR (600 MHz, DMSO-d_6) δ (ppm) 7.83 (d, *J* = 7.8 Hz, 2H), 7.44 – 7.39 (m, 3H), 7.20 (t, *J* = 7.2 Hz, 1H), 6.92 (d, *J* = 3.0 Hz, 1H), 6.69 (s, 1H), 6.36 (d, *J* = 5.4 Hz, 1H), 5.70 (d, *J* = 8.4 Hz, 1H), 4.30 (dd, *J* = 10.8, 6.0 Hz, 1H), 4.19 – 4.14 (m, 2H), 3.59 (t, *J* = 5.4 Hz, 1H), 2.78 – 2.70 (m, 1H), 1.95 (s, 3H), 1.25 (t, *J* = 6.6 Hz, 3H), 0.98 (d, *J* = 6.6 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (150 MHz, DMSO-d_6) δ (ppm) 172.4, 171.8, 162.2, 141.2, 138.6, 129.6, 129.4, 128.2, 126.3, 125.2, 123.9, 118.8, 69.8, 66.0, 61.1, 48.1, 29.9, 14.7, 14.6, 14.2; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{23}H_{24}SN_2O_4Na$ 447.1354; found 447.1354.

Ethyl-(5*S*,8*R*,9*R*,10*S*)-1,9-dimethyl-4-oxo-3-phenyl-6-(thiophen-2-yl)-10-((trimethyl-

silyl)oxy)-2,3-diazaspiro[4.5]deca-1,6-diene-8-carboxylate (4i): oil, 58.1 mg, 78% yield, dr 83:17, *ee* 93%, $[\alpha]_D^{20}$ = +48.3 (*c* = 0.26 in CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.92 – 7.90 (m, 2H), 7.38 (t, *J* = 7.8 Hz, 2H), 7.18 – 7.15 (m, 1H), 7.07 – 7.06 (m, 1H), 6.80 (dd, *J* = 4.8, 3.6 Hz, 1H), 6.67 (dd, *J* = 3.6, 1.2 Hz, 1H), 6.35 (d, *J* = 6.0 Hz, 1H), 4.66 (d, *J* = 11.4 Hz, 1H), 4.23 – 4.17 (m, 2H), 3.52 (t, *J* = 6.0 Hz, 1H), 2.93 (ddd, *J* = 11.4, 6.6, 6.0 Hz, 1H), 1.99 (s, 3H), 1.31 (t, *J* = 7.2 Hz, 3H), 1.02 (d, *J* = 7.2 Hz, 3H), 0.02 (s, 9H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ (ppm) 172.4, 172.0, 161.5, 140.7, 138.2, 129.7, 128.9, 128.9, 127.8, 125.0, 124.9, 123.8, 118.9, 72.8, 66.0, 61.2, 48.4, 30.6, 15.2, 14.5, 14.5, 0.8; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{26}H_{32}SN_2O_4SiNa$ 519.1750; found 519.1748.

Ethyl-(5*S*,8*R*,9*R*,10*S*)-10-hydroxy-1,9-dimethyl-6-(naphthalen-2-yl)-4-oxo-3-phenyl-2,3-diazaspiro[4.5]deca-1,6-diene-8-carboxylate (3j): white solid, 54.8 mg, 78% yield, dr 68:32, m.p. 79-80 °C; $[\alpha]_D^{20}$ = +15.2 (*c* = 0.13 in CH_2Cl_2); ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm) 7.82 (dd, *J* = 9.0, 1.2 Hz, 2H), 7.81 – 7.80 (m, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.62 – 7.61 (m, 1H), 7.48 (d, *J* = 1.2 Hz, 1H), 7.45 – 7.40 (m, 4H), 7.22 – 7.19 (m, 1H), 7.08 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.20 (d, *J* = 2.4 Hz, 1H), 5.78 (d, *J* = 6.6 Hz, 1H), 4.14 – 4.10 (m, 2H), 3.80 (dd, *J* = 11.4, 6.6 Hz, 1H), 3.23 (dd, *J* = 10.2, 2.4 Hz, 1H), 2.92 – 2.88 (m, 1H), 1.71 (s, 3H), 1.18 (t, *J* = 7.2 Hz, 3H), 1.02 (d, *J* = 6.6 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6) δ (ppm) 172.7, 172.4, 162.4, 138.6, 136.9, 134.4, 133.1, 132.8, 131.0, 129.6, 128.8, 128.3, 128.0, 127.2, 126.9, 125.3, 125.2, 124.4, 118.8, 73.3, 65.5, 61.2, 50.4, 30.2, 16.3, 14.7, 14.5; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{29}H_{28}N_2O_4Na$ 491.1947; found 491.1949.

Ethyl-(5*S*,8*R*,9*R*,10*S*)-1,9-dimethyl-6-(naphthalen-2-yl)-4-oxo-3-phenyl-10-((trimethyl-silyl)oxy)-2,3-diazaspiro[4.5]deca-1,6-diene-8-carboxylate (4j): oil, 55.9 mg, 69% yield, dr 68:32, *ee* 99%, $[\alpha]_D^{20}$ = +16.6 (*c* = 0.17 in CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.92 (d, *J* = 7.8 Hz, 2H), 7.74 (d, *J* = 7.2 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.65 – 7.61 (m, 2H), 7.52 (s, 1H), 7.45 – 7.43 (m, 3H), 7.23 – 7.19 (m, 2H), 6.27 (d, *J* = 4.8 Hz, 1H), 4.71 (d, *J* = 11.4 Hz, 1H), 4.30 – 4.24 (m, 2H), 3.63 (t, *J* = 5.4 Hz, 1H), 3.18 – 3.14 (m, 1H), 1.87 (s, 3H), 1.37 (t, *J* = 7.2 Hz, 3H), 1.10 (d, *J* = 6.6 Hz, 3H), 0.05 (s, 9H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ

(ppm) 172.8, 172.4, 161.0, 138.1, 136.5, 136.4, 133.1, 132.8, 129.8, 128.8, 128.3, 128.1, 127.5, 126.3, 126.2, 125.5, 125.0, 124.6, 119.2, 72.8, 66.2, 61.0, 48.4, 30.2, 15.1, 14.5, 14.4, 0.7; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{32}H_{36}N_2O_4SiNa$ 563.2342; found 563.2339.

Ethyl-1,9-dimethyl-6-(naphthalen-2-yl)-4-oxo-3-phenyl-10-((trimethylsilyl)oxy)-2,3-diazaspiro[4.5]deca-1,6-diene-8-carboxylate (4j'): oil, 15.4 mg, 19% yield, dr 32:68, *ee* 7%, ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.96 (dd, *J* = 9.0, 1.2 Hz, 2H), 7.76 – 7.74 (m, 1H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.63 – 7.61 (m, 1H), 7.50 (d, *J* = 1.8 Hz, 1H), 7.46 – 7.43 (m, 2H), 7.43 – 7.41 (m, 2H), 7.23 (tt, *J* = 7.8, 1.2 Hz, 1H), 7.18 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.29 (d, *J* = 2.4 Hz, 1H), 4.26 – 4.18 (m, 2H), 3.91 (d, *J* = 10.8 Hz, 1H), 3.32 – 3.26 (m, 1H), 3.11 (dd, *J* = 10.8, 2.4 Hz, 1H), 1.77 (s, 3H), 1.60 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.12 (d, *J* = 6.6 Hz, 3H), 0.06 (s, 9H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ (ppm) 172.3, 171.9, 160.4, 138.2, 136.3, 134.8, 133.1, 132.8, 130.4, 128.9, 128.4, 128.1, 127.5, 126.4, 126.2, 125.3, 125.0, 124.3, 119.1, 76.7, 65.5, 61.3, 50.8, 30.6, 16.9, 14.7, 14.2, 0.8; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{32}H_{36}N_2O_4SiNa$ 563.2342; found 563.2345.

Ethyl-(5*S*,8*R*,9*R*,10*S*)-3-(2-fluorophenyl)-10-hydroxy-1,9-dimethyl-4-oxo-6-phenyl-2,3-diazaspiro[4.5]deca-1,6-diene-8-carboxylate (3k): white solid, 53.7 mg, 82% yield, dr 62:38, m.p. 177-178 °C; $[\alpha]_D^{20}$ = +32.6 (*c* = 0.21 in CH_2Cl_2); ^1H NMR (600 MHz, DMSO-d_6) δ (ppm) 7.42 – 7.41 (m, 2H), 7.31 (dd, *J* = 5.4, 1.8 Hz, 3H), 7.29 (dd, *J* = 4.8, 1.8 Hz, 2H), 7.14 (dd, *J* = 6.0, 2.4 Hz, 2H), 6.09 (d, *J* = 2.4 Hz, 1H), 5.79 (d, *J* = 6.0 Hz, 1H), 4.16 – 4.12 (m, 2H), 3.80 (dd, *J* = 10.8, 6.0 Hz, 1H), 3.21 (dd, *J* = 10.2, 2.4 Hz, 1H), 2.88 – 2.82 (m, 1H), 1.71 (s, 3H), 1.21 (t, *J* = 7.2 Hz, 3H), 1.04 (d, *J* = 6.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, DMSO-d_6) δ (ppm) 172.2, 171.7, 161.5, 156.1 (d, J_{CF} = 250.5 Hz), 138.8, 133.9, 129.8, 129.2, 128.5, 127.2 (d, J_{CF} = 0.8 Hz), 126.7, 125.8, 124.7 (d, J_{CF} = 3.5 Hz), 116.6 (d, J_{CF} = 19.7 Hz), 72.5, 63.1, 60.5, 49.6, 29.4, 15.7, 14.0, 13.8; ^{19}F NMR (565 MHz, DMSO-d_6) δ (ppm) -118.87; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{25}H_{25}FN_2O_4Na$ 459.1696; found 459.1693.

Ethyl-(5*S*,8*R*,9*R*,10*S*)-3-(2-fluorophenyl)-1,9-dimethyl-4-oxo-6-phenyl-10-((trimethyl silyl)oxy)-2,3-diazaspiro[4.5]deca-1,6-diene-8-carboxylate (4k): oil, 56.5 mg, 74% yield, dr 62:38, *ee* 95%, $[\alpha]_D^{20}$ = +17.3 (*c* = 0.30 in CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.46 (td, *J* = 7.8, 1.8 Hz, 1H), 7.35 – 7.31 (m, 1H), 7.27 – 7.26 (m, 2H), 7.23 – 7.20 (m, 2H), 7.17 – 7.15 (m, 2H), 6.15 (d, *J* = 2.4 Hz, 1H), 4.23 – 4.15 (m, 2H), 3.89 (d, *J* = 10.8 Hz, 1H), 3.30 – 3.23 (m, 1H), 3.06 (dd, *J* = 10.8, 2.4 Hz, 1H), 1.78 (s, 3H), 1.26 (d, *J* = 7.2 Hz, 3H), 1.11 (d, *J* = 6.6 Hz, 3H), 0.13 (s, 9H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ (ppm) 172.5, 171.9, 160.7, 157.0 (d, J_{CF} = 252.0 Hz), 139.0, 134.8, 130.1, 129.3 (d, J_{CF} = 8.0 Hz), 128.7, 128.2, 127.1 (d, J_{CF} = 1.4 Hz), 126.5, 125.1 (d, J_{CF} = 12.2 Hz), 124.4 (d, J_{CF} = 4.1 Hz), 117.0 (d, J_{CF} = 19.5 Hz), 64.1, 61.3, 50.9, 30.6, 16.9, 14.7, 14.3, 0.9; ^{19}F NMR (565 MHz, DMSO-d_6) δ (ppm) -118.40; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{28}H_{33}FN_2O_4SiNa$ 531.2091; found 531.2090.

Ethyl-3-(2-fluorophenyl)-1,9-dimethyl-4-oxo-6-phenyl-10-((trimethylsilyl)oxy)-2,3-diazaspiro[4.5]deca-1,6-diene-8-carboxylate (4k'): white solid, 8.4 mg, 11% yield, dr 38:62, *ee* 82%, m.p. 153-154 °C; $[\alpha]_D^{20}$ = -49.8 (*c* = 0.11 in CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.46 (td, *J* = 7.2, 1.2 Hz, 1H), 7.35 – 7.31 (m, 1H), 7.27 – 7.26 (m, 2H), 7.24 – 7.22 (m, 2H), 7.21 – 7.19 (m, 1H), 7.17 – 7.15 (m, 2H), 6.15 (d, *J* = 2.4 Hz, 1H), 4.23 – 4.15 (m, 2H), 3.89 (d, *J* = 10.8 Hz, 1H), 3.30 – 3.23 (m, 1H), 3.06 (dd, *J* = 10.8, 3.0 Hz, 1H), 1.78 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.10 (d, *J* = 6.6 Hz, 3H), 0.13 (s, 9H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ (ppm) 172.4, 171.8, 160.6, 156.89 (d, J_{CF} = 251.7 Hz), 138.9, 134.7, 130.0, 129.2 (d, J_{CF} = 7.8 Hz), 128.6, 128.3, 128.1, 127.1 (d, J_{CF} = 1.1 Hz), 126.4, 124.3 (d, J_{CF} = 4.1 Hz), 116.9 (d, J_{CF} = 19.5 Hz), 76.5, 63.9, 61.2, 50.8, 30.5, 16.8, 14.7, 14.2, 0.8; ^{19}F NMR (565 MHz, $CDCl_3$) δ (ppm) -118.03; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{28}H_{33}FN_2O_4SiNa$ 531.2091; found 531.2094.

Ethyl-(5*S*,8*R*,9*R*,10*S*)-3-(3-chlorophenyl)-10-hydroxy-1,9-dimethyl-4-oxo-6-phenyl-2,3-diazaspiro[4.5]deca-1,6-diene-8-carboxylate (3l): white solid, 54.4 mg, 80% yield, dr 60:40, m.p. 169-170 °C; $[\alpha]_D^{20}$ = 25.4 (*c* = 0.16 in CH_2Cl_2); ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm) 7.80 (d, *J* = 8.4 Hz, 2H), 7.35 – 7.32 (m, 2H), 7.31 – 7.29 (m, 1H), 7.14 – 7.11 (m, 2H), 7.05

(dd, *J* = 5.4, 1.2 Hz, 1H), 6.98 (t, *J* = 7.2 Hz, 1H), 6.07 (d, *J* = 2.4 Hz, 1H), 5.78 (d, *J* = 6.0 Hz, 1H), 4.19 – 4.13 (m, 2H), 3.82 (dd, *J* = 11.4, 6.6 Hz, 1H), 3.28 (dd, *J* = 10.2, 2.4 Hz, 1H), 3.00 – 2.92 (m, 2H), 1.81 (s, 3H), 1.21 (t, *J* = 7.2, 3H), 1.06 (d, *J* = 6.6 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (150 MHz, DMSO-d_6) δ 174.1, 172.0, 161.3, 160.4, 158.3, 138.6, 133.2, 130.6, 129.9, 129.4, 128.3, 126.7, 125.0, 118.6, 116.4, 73.2, 65.4, 61.2, 50.3, 33.8, 16.4, 14.6, 14.6; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{25}H_{25}ClN_2O_4Na$ 475.1401; found 475.1399.

Ethyl-(5*S*,8*R*,9*R*,10*S*)-3-(3-chlorophenyl)-1,9-dimethyl-4-oxo-6-phenyl-10-((trimethyl silyl)oxy)-2,3-diazaspiro[4.5]deca-1,6-diene-8-carboxylate (4l): oil, 56.7 mg, 72% yield, dr 60:40, *ee* 94%, $[\alpha]_D^{20}$ = +13.6 (*c* = 0.21 in CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.99 (t, *J* = 2.4 Hz, 1H), 7.87 (dd, *J* = 8.4 1.2 Hz, 1H), 7.33 (t, *J* = 8.4 Hz, 1H), 7.24 – 7.19 (m, 3H), 7.17 – 7.15 (m, 1H), 7.03 (dd, *J* = 7.8, 1.2 Hz, 2H), 6.14 (d, *J* = 5.4 Hz, 1H), 4.65 (d, *J* = 10.8 Hz, 1H), 4.27 – 4.21 (m, 2H), 3.57 (t, *J* = 6.0 Hz, 1H), 3.08 – 3.01 (m, 1H), 1.87 (s, 3H), 1.35 (t, *J* = 7.2 Hz, 3H), 1.06 (d, *J* = 7.2 Hz, 3H), 0.02 (s, 9H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ (ppm) 172.9, 172.4, 161.5, 139.2, 138.9, 136.4, 134.7, 130.0, 129.7, 128.8, 128.3, 126.6, 124.9, 118.7, 116.6, 72.9, 66.4, 61.1, 48.4, 30.3, 15.2, 14.6, 14.5, 0.8; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{28}H_{33}ClN_2O_4SiNa$ 547.1796; found 547.1799.

Ethyl-3-(3-chlorophenyl)-1,9-dimethyl-4-oxo-6-phenyl-10-((trimethylsilyl)oxy)-2,3-diazaspiro[4.5]deca-1,6-diene-8-carboxylate (4l'): oil, 7.9 mg, 10% yield, dr 40:60, *ee* 4%, ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.05 (t, *J* = 1.8 Hz, 1H), 7.90 (ddd, *J* = 8.4, 2.4, 1.2 Hz, 1H), 7.33 (t, *J* = 7.8 Hz, 1H), 7.24 – 7.20 (m, 3H), 7.17 – 7.15 (m, 1H), 7.01 (d, *J* = 7.8, 1.2 Hz, 2H), 6.16 (d, *J* = 2.4 Hz, 1H), 4.26 – 4.19 (m, 2H), 3.85 (d, *J* = 10.8 Hz, 1H), 3.24 – 3.17 (m, 1H), 3.06 (dd, *J* = 10.2, 2.4 Hz, 1H), 1.78 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.09 (d, *J* = 6.6 Hz, 3H), 0.04 (s, 9H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ (ppm) 172.2, 171.8, 160.8, 139.3, 138.8, 134.6, 134.5, 130.1, 129.9, 128.7, 128.1, 126.2, 124.7, 118.5, 116.4, 99.9, 76.7, 65.6, 61.3, 50.6, 30.5, 16.9, 14.7, 14.2, 0.8; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{28}H_{33}ClN_2O_4SiNa$ 547.1796; found 547.1795.

Ethyl-(5*S*,8*R*,9*R*,10*S*)-10-hydroxy-1,9-dimethyl-4-oxo-6-phenyl-3-(p-tolyl)-2,3-diaza-spiro[4.5]deca-1,6-diene-8-carboxylate (3m): white solid, 52.6 mg, 81% yield, dr 65:35, m.p. 176-177 °C; $[\alpha]_D^{20}$ = -8.6 (*c* = 0.17 in CH_2Cl_2); ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm) 7.68 (d, *J* = 7.8 Hz, 2H), 7.26 – 7.23 (m, 5H), 6.97 – 6.96 (m, 2H), 6.10 (d, *J* = 4.8 Hz, 1H), 5.62 (d, *J* = 6.0 Hz, 1H), 4.28 (dd, *J* = 11.4, 6.6 Hz, 1H), 4.21 – 4.14 (m, 2H), 3.56 (t, *J* = 5.4 Hz, 1H), 2.88 – 2.84 (m, 1H), 2.31 (s, 3H), 1.79 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H), 0.99 (d, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6) δ (ppm) 172.7, 172.1, 161.9, 139.5, 136.3, 136.2, 134.4, 129.9, 129.8, 129.1, 128.6, 126.6, 118.8, 69.8, 65.9, 61.1, 48.2, 29.5, 21.0, 14.7, 14.6, 14.3; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{26}H_{28}N_2O_4Na$ 455.1947; found 455.1949.

Ethyl-(5*S*,8*R*,9*R*,10*S*)-1,9-dimethyl-4-oxo-6-phenyl-3-(p-tolyl)-10-((trimethylsilyl)oxy)-2,3-diazaspiro[4.5]deca-1,6-diene-8-carboxylate (4m): white solid, 54.5 mg, 72% yield, dr 65:35, *ee* 99%, m.p. 144-145 °C; $[\alpha]_D^{20}$ = -26.9 (*c* = 0.34 in CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.77 (d, *J* = 8.4 Hz, 2H), 7.22 (br, s, 1H), 7.21 – 7.18 (m, 4H), 7.06 – 7.04 (m, 2H), 6.13 (d, *J* = 5.4 Hz, 1H), 4.64 (d, *J* = 10.8 Hz, 1H), 4.26 – 4.21 (m, 2H), 3.57 (t, *J* = 5.4 Hz, 1H), 3.12 – 3.06 (m, 1H), 2.36 (s, 3H), 1.86 (s, 3H), 1.35 (t, *J* = 7.2 Hz, 3H), 1.06 (d, *J* = 7.2 Hz, 3H), 0.03 (s, 9H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ (ppm) 172.6, 172.5, 160.9, 139.1, 136.7, 135.8, 134.7, 129.4, 129.4, 128.6, 128.2, 126.7, 119.2, 72.8, 66.2, 61.1, 48.5, 30.3, 21.1, 15.2, 14.3, 14.5, 0.9; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{29}H_{36}N_2O_4SiNa$ 527.2342; found 527.2339.

Ethyl-1,9-dimethyl-4-oxo-6-phenyl-3-(p-tolyl)-10-((trimethylsilyl)oxy)-2,3-diazaspiro-[4.5]deca-1,6-diene-8-carboxylate (4m'): oil, 10.6 mg, 14% yield, dr 35:65, *ee* 25%, $[\alpha]_D^{20}$ = -14.2 (*c* = 0.12 in CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.82 (d, *J* = 8.4 Hz, 2H), 7.22 – 7.20 (m, 4H), 7.20 – 7.19 (m, 1H), 7.04 (dd, *J* = 7.8, 1.2 Hz, 2H), 6.15 (d, *J* = 2.4 Hz, 1H), 4.26 – 4.17 (m, 2H), 3.85 (d, *J* = 10.8 Hz, 1H), 3.27 – 3.21 (m, 1H), 3.05 (dd, *J* = 10.2, 2.4 Hz, 1H), 2.37 (s, 3H), 1.78 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.08 (d, *J* = 6.6 Hz, 3H), 0.05 (s, 9H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ (ppm) 171.9, 160.1, 138.9, 135.8, 134.8, 134.5, 129.9,

129.3, 128.6, 128.0, 126.3, 118.9, 76.7, 65.3, 61.2, 50.7, 30.5, 21.0, 16.9, 14.6, 14.2, 0.8; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{29}H_{36}N_2O_4SiNa$ 527.2342; found 527.2340.

Ethyl-(5*S*,8*R*,9*R*,10*S*)-10-hydroxy-9-methyl-4-oxo-1,3,6-triphenyl-2,3-diazaspiro[4.5]-deca-1,6-diene-8-carboxylate (3n): white solid, 61.3 mg, 85% yield, dr 85:15, m.p. 154-155 ^oC; $[\alpha]_D^{20}$ = -13.8 (*c* = 0.18 in CH_2Cl_2); ^1H NMR (600 MHz, DMSO-d_6) δ (ppm) 8.00 (dd, *J* = 6.0, 1.8 Hz, 2H), 7.95 (d, *J* = 8.4 Hz, 2H), 7.51 – 7.48 (m, 2H), 7.38 (d, *J* = 6.0 Hz, 3H), 7.27 (t, *J* = 7.2 Hz, 1H), 7.12 (d, *J* = 5.4 Hz, 3H), 6.97 – 6.96 (m, 2H), 6.23 (d, *J* = 4.8 Hz, 1H), 5.66 (dd, *J* = 6.0, 3.0 Hz, 1H), 4.55 (dd, *J* = 10.8, 6.0 Hz, 1H), 4.27 – 4.21 (m, 2H), 3.69 (t, *J* = 6.0 Hz, 1H), 3.01 – 2.95 (m, 1H), 1.29 (t, *J* = 7.2 Hz, 3H), 0.98 (d, *J* = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, DMSO-d_6) δ (ppm) 173.1, 172.3, 158.7, 139.4, 138.5, 137.7, 130.8, 130.2, 129.6, 129.2, 129.0, 128.9, 128.4, 126.9, 126.6, 125.7, 119.3, 71.6, 64.8, 61.2, 48.4, 29.6, 14.9, 14.6; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{30}H_{28}N_2O_4Na$ 503.1947; found 503.1946.

Ethyl-(5*S*,8*R*,9*R*,10*S*)-9-methyl-4-oxo-1,3,6-triphenyl-10-((trimethylsilyl)oxy)-2,3-diaza-spiro[4.5]deca-1,6-diene-8-carboxylate (4n): oil, 63.8 mg, 77% yield, dr 85:15, *ee* 96%, $[\alpha]_D^{20}$ = -37.2 (*c* = 0.11 in CH_2Cl_2); ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.05 – 8.03 (m, 2H), 8.01 – 7.99 (m, 2H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.35 – 7.31 (m, 3H), 7.21 – 7.19 (m, 1H), 7.05 – 7.00 (m, 3H), 6.99 (dd, *J* = 7.8, 1.2 Hz, 2H), 6.14 (d, *J* = 5.4 Hz, 1H), 4.91 (d, *J* = 10.8 Hz, 1H), 4.28 (qd, *J* = 7.2, 1.2 Hz, 2H), 3.68 (t, *J* = 6.0 Hz, 1H), 3.26 – 3.19 (m, 1H), 1.35 (t, *J* = 7.2 Hz, 3H), 1.03 (d, *J* = 7.2 Hz, 3H), -0.26 (s, 9H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ (ppm) 173.0, 172.6, 157.8, 138.9, 138.7, 138.3, 130.4, 130.1, 129.0, 128.6, 128.4, 128.1, 128.0, 126.9, 126.8, 125.3, 119.4, 74.9, 65.2, 61.1, 48.8, 29.8, 15.1, 14.6, 0.5; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{33}H_{36}N_2O_4SiNa$ 575.2342; found 575.2339.

Ethyl-(5*S*,8*R*,9*R*,10*S*)-9-ethyl-10-hydroxy-1-methyl-4-oxo-3,6-diphenyl-2,3-diazaspiro-[4.5]deca-1,6-diene-8-carboxylate (3o): white solid, 57.1 mg, 88% yield, dr 86:14, m.p. 180-181 ^oC; $[\alpha]_D^{20}$ = -16.9 (*c* = 0.32 in CH_2Cl_2); ^1H NMR (600 MHz, DMSO-d_6) δ (ppm) 7.81 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.44 (dd, *J* = 8.4, 7.8 Hz, 2H), 7.26 – 7.24 (m, 3H), 7.22 – 7.19 (m, 1H),

6.99 – 6.97 (m, 2H), 6.15 (d, *J* = 5.4 Hz, 1H), 5.70 (d, *J* = 6.0 Hz, 1H), 4.38 (dd, *J* = 11.4, 6.6 Hz, 1H), 4.24 – 4.19 (m, 1H), 4.17 – 4.13 (m, 1H), 3.69 (t, *J* = 5.4 Hz, 1H), 2.64 – 2.53 (m, 1H), 1.80 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.00 – 0.70 (m, 4H), 0.88 – 0.81 (m, 1H); $^{13}C\{^{1}H\}$ NMR (150 MHz, DMSO-d_6) δ (ppm) 173.0, 172.0, 162.1, 139.4, 138.5, 136.1, 130.0, 129.5, 129.2, 128.6, 126.6, 125.2, 118.7, 69.1, 66.1, 61.1, 45.2, 36.6, 21.1, 14.7, 14.3, 12.0; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{26}H_{28}N_2O_4Na$ 455.1947; found 455.1949.

Ethyl-(5*S*,8*R*,9*R*,10*S*)-9-ethyl-1-methyl-4-oxo-3,6-diphenyl-10-((trimethylsilyl)oxy)-2,3-diazaspiro[4.5]deca-1,6-diene-8-carboxylate (4o): oil, 60.6 mg, 80% yield, dr 86:14, *ee* 95%, $[\alpha]_D^{20}$ = -33.6 (*c* = 0.43 in CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.90 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.41 (dd, *J* = 9.0, 7.8 Hz, 2H), 7.23 – 7.19 (m, 4H), 7.06 (dd, *J* = 7.8, 1.2 Hz, 2H), 6.18 (d, *J* = 5.4 Hz, 1H), 4.74 (d, *J* = 10.8 Hz, 1H), 4.29 – 4.20 (m, 2H), 3.74 (t, *J* = 5.4 Hz, 1H), 2.88 – 2.83 (m, 1H), 1.87 (s, 3H), 1.35 (t, *J* = 7.2 Hz, 3H), 1.11 – 0.95 (m, 5H), 0.03 (s, 9H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ (ppm) 172.9, 172.3, 161.1, 139.0, 138.2, 136.6, 129.5, 128.9, 128.7, 128.2, 126.7, 125.0, 119.2, 72.4, 66.4, 61.1, 44.9, 37.1, 21.4, 14.6, 14.5, 11.4, 0.8; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{29}H_{36}N_2O_4SiNa$ 527.2342; found 527.2341.

Ethyl-(5*S*,8*R*,9*R*,10*S*)-10-hydroxy-1-methyl-9-(2-methylprop-1-en-1-yl)-4-oxo-3,6-diphenyl-2,3-diazaspiro[4.5]deca-1,6-diene-8-carboxylate (3p): oil, 53.7 mg, 78% yield, dr 80:20, $[\alpha]_D^{20}$ = -19.3 (*c* = 0.14 in CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.92 (dd, *J* = 8.4, 0.6 Hz, 2H), 7.42 (dd, *J* = 8.4, 7.8 Hz, 2H), 7.24 – 7.23 (m, 1H), 7.21 – 7.19 (m, 3H), 7.06 (dd, *J* = 7.8, 1.2 Hz, 2H), 6.13 (d, *J* = 4.8 Hz, 1H), 5.05 (d, *J* = 10.2 Hz, 1H), 4.60 (dd, *J* = 10.8, 3.0 Hz, 1H), 4.31 – 4.25 (m, 1H), 4.23 – 4.19 (m, 1H), 4.01 (td, *J* = 10.2, 6.0 Hz, 1H), 3.61 (t, *J* = 5.4 Hz, 1H), 1.90 (s, 3H), 1.81 (d, *J* = 3.0 Hz, 1H), 1.80 (s, 3H), 1.78 (s, 3H); 1.33 (d, *J* = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ (ppm) 172.2, 172.0, 161.3, 141.4, 138.6, 136.4, 129.0, 128.8, 128.6, 128.2, 126.5, 125.1, 119.6, 119.2, 68.8, 64.5, 61.0, 47.0, 34.7, 26.2, 18.7, 14.4, 14.0; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{28}H_{30}N_2O_4Na$ 481.2103; found 481.2101.

Ethyl-(5*S*,8*R*,9*R*,10*S*)-1-methyl-9-(2-methylprop-1-en-1-yl)-4-oxo-3,6-diphenyl-10-((trimethylsilyl)oxy)-2,3-diazaspiro[4.5]deca-1,6-diene-8-carboxylate (4p): oil, 55.7 mg, 70% yield, dr 80:20, *ee* 66%, $[\alpha]_D^{20}$ = -41.2 (*c* = 0.08 in CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.89 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.43 – 7.40 (m, 2H), 7.22 – 7.18 (m, 4H), 7.07 – 7.05 (m, 2H), 6.14 (d, *J* = 5.4 Hz, 1H), 4.95 (dd, *J* = 9.6, 1.2 Hz, 1H), 4.80 (d, *J* = 10.8 Hz, 1H), 4.28 – 4.18 (m, 2H), 3.90 (td, *J* = 10.8, 6.0 Hz, 1H), 3.56 (t, *J* = 5.4 Hz, 1H), 1.86 (s, 3H), 1.73 – 1.72 (m, 6H), 1.34 (t, *J* = 7.2 Hz, 3H), -0.03 (s, 9H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ (ppm) 172.7, 172.5, 160.8, 139.1, 138.3, 137.4, 136.6, 129.3, 128.9, 128.7, 128.2, 126.6, 124.9, 122.3, 119.3, 71.6, 66.2, 61.0, 47.8, 35.3, 26.3, 18.6, 14.5, 14.5, 0.7; HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{31}H_{38}N_2O_4SiNa$ 553.2499; found 553.2501.

Procedure for the asymmetric synthesis of 5a

To a solution of **3a** in dichloromethane (5 mL) was added PCC (107.8 mg, 0.5 mmol). The mixture was stirred for 2 h at 40 °C in oil bath. The solid was removed by filtration through celite. The residue was purified by chromatography on silica gel (*n*-hexane/ethyl acetate = 5:1) to give product **5a** which was dried under vacuum and further analyzed by ^{1}H-NMR, ^{13}C-HMR, HRMS, chiral HPLC analysis, *etc*.

Ethyl-(5*S*,8*R*,9*R*)-1,9-dimethyl-4,10-dioxo-3,6-diphenyl-2,3-diazaspiro[4.5]deca-1,6-diene-8-carboxylate (5a): oil, 48.7 mg, 78% yield, dr 83:17, *ee* 94%, m.p. 175-176 °C; $[\alpha]_D^{20}$ = +17.2 (*c* = 0.19 in CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.81 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.41 – 7.38 (m, 2H), 7.29 – 7.27 (m, 1H), 7.25 – 7.20 (m, 3H), 7.13 – 7.10 (m, 2H), 6.38 (d, *J* = 6.0 Hz, 1H), 4.27 – 4.19 (m, 2H), 3.85 (t, *J* = 6.0 Hz, 1H), 3.62 – 3.57 (m, 1H), 2.00 (s, 3H), 1.31 (t, *J* = 7.2 Hz, 3H), 1.17 (d, *J* = 6.6 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ (ppm) 197.9, 171.1, 168.1, 160.5, 138.5, 137.7, 137.7, 129.0, 129.0, 128.9, 128.6, 126.8, 125.8, 119.5, 74.6, 61.9, 50.4, 41.7, 15.4, 14.4, 11.4; HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{25}H_{24}N_2O_4Na$ 439.1634; found 439.1632.

ASSOCIATED CONTENT

Supporting information

The Supporting Information is available free of charge on the ACS Publications website at http://pubs.acs.org.

Crystal data of **4m** and **4k'**

^{1}H and $^{13}C\{^{1}H\}$ NMR spectra for substrates **1**

^{1}H and $^{13}C\{^{1}H\}$ NMR spectra, HPLC chromatograms, products **3**, **4**, **5a** and some of diastereoisomers of **4'**.

The anti-proliferative IC50 values against a panel of cancer cell lines (Table S1)

AUTHOR INFORMATION

Corresponding Authors

*E-mail: hanbo@cdutcm.edu.cn.

*E-mail: *hegu@scu.edu.cn*

ORCID

Bo Han: 0000-0003-3200-4682

Notes

The authors declare no competing financial interest

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