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Asymmetric Synthesis

Optically Active 4-Substituted 5-Nitropentan-2-ones: Valuable Chiral Building Blocks for the Stereocontrolled Construction of Spiro-Pyrazolone Scaffolds with Five Contiguous Stereogenic Centers

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Abstract: The application of readily available optically active 4-substituted 5-nitropentan-2-ones as chiral building blocks in the stereocontrolled construction of spiro-pyrazolone scaffolds was investigated. In the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (1 equiv.) optically active 4-substituted 5-nitropentan-4-ones exhibited excellent chiral inducing abilities in the diastereoselective cascade Michael/aldol reaction with a wide range of unsaturated pyrazolones to generate the corresponding biologically significant spiro-pyrazolone derivatives with five contiguous stereocenters in acceptable to good yield with high levels of diastereoselectivity.

Introduction

Pyrazolones are an important class of heterocyclic compounds that occur in many drugs and synthetic products (Figure 1).[1] Pyrazolone derivatives are associated with a broad range of biological activities, which includes antimicrobial,[2] analgesic,[2a,3] antitubercular,[4] antibacterial,[5] anti-inflammatory,[2a] antioxidant,[2b,5e,6] and anticancer activities.[2b,5c,7] Owing to the broad biological activities and extensive application of pyrazolone compounds, the development of asymmetric methods for the synthesis of chiral pyrazolone derivatives is of considerable interest. Pyrazolones are excellent nucleophiles in various carbon–carbon bond-forming reactions,[8] and the most convenient access to chiral pyrazolone derivatives is the catalytic asymmetric direct functionalization of achiral pyrazolones through metal[9] or organocatalyzed[10] nucleophilic addition reactions. An alternative synthesis of chiral pyrazolone derivatives is the use of unsaturated pyrazolones as electrophiles in organocatalytic cascade sequences. In these cases, the construction of multi-stereogenic spiro-pyrazolone scaffolds was achieved in enantioselective fashion.[11] Despite the substantial advances made thus far, the synthetic challenge of the spiro motif continues to encourage the development of creative and efficient methods to access these important spirocyclic structures from readily available starting materials in an atom- and step-economic manner. Recently, we found that primary amine-thiophosphinamide **1** is a highly efficient recyclable catalyst for the Michael addition reaction of acetone to simple β-nitrostyrene. Under catalysis with **1**, almost enantiomerically pure 4-substituted 5-nitropentan-2-ones **2** were conveniently obtained on a 10-gram scale (Scheme 1, Equation 1).[12] Can these types of readily available compounds serve as valuable chiral building blocks to induce highly diastereoselective reactions to access other chiral complex structures? By considering the high reactivity of unsaturated pyrazolones **3** and the importance of spiro-pyrazolone derivatives, we envisioned that the construction of highly functionalized spiro-pyrazolone scaffolds **4** with five contiguous stereogenic centers may be conveniently achieved through achiral Brønsted-base-promoted diastereoselective cascade Michael/aldol reaction between **2** and **3** (Scheme 1, Equation 2).[13,14]

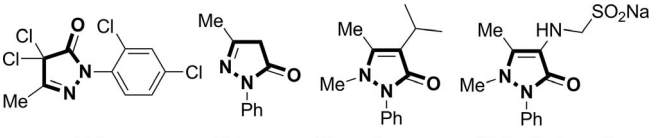

Figure 1. Biologically important pyrazolones.

Results and Discussion

The present studies were initiated by treating (*R*)-4-(4-chlorophenyl)-5-nitropentan-2-one (**2a**) with pyrazolone-derived activated alkene **3a** in dichloromethane at room temperature under Brønsted base mediated conditions (Table 1). All of the screened bases, which include both organic and inorganic bases, promote the model reaction smoothly to provide annulation product **4aa** in acceptable yields. However, the efficacy and diastereoselectivity of the reaction are somewhat dependent

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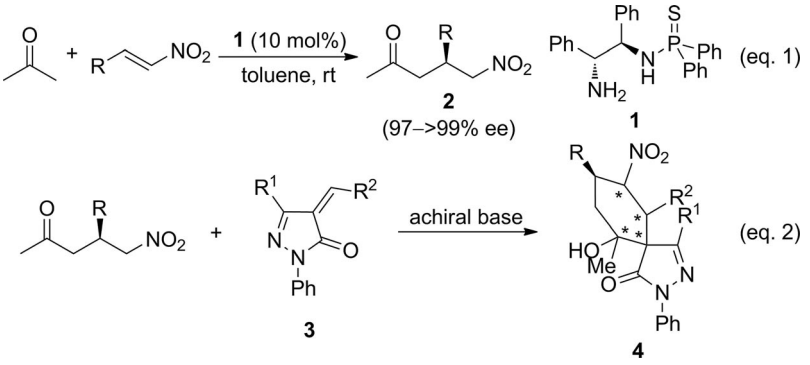
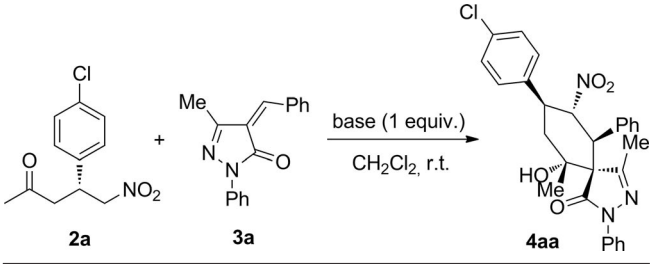


Scheme 1. Construction of spiro-pyrazolones through chiral nitroalkanone-induced diastereoselective cascade Michael/aldol reaction.

on the base employed. For example, the use of Et_3N, 1,4-diazabicyclo[2.2.2]octane (DABCO), diisopropylethylamine (DIPEA), 4-(dimethylamino)pyridine (DMAP), and *N*,*N*,*N*′,*N*′-tetramethylethane-1,2-diamine (TMEDA) resulted in complete conversion of unsaturated pyrazolone **3a** over 96 h to afford spiro-pyrazolone **4aa** in 60–80 % yield with diastereomeric ratios in the range 16:1 to >20:1 (Table 1, Entries 1–5). More basic amidine and guanidine bases, such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and tetramethylguanidine (TMG) proved more efficient for this transformation by delivering corresponding product **4aa** with high diastereoselectivities within two hours (Table 1, Entries 6 and 7). Inorganic bases, such as sodium hydroxide and potassium carbonate, can also promote the model reaction efficiently, albeit in slightly decreased yields (Table 1, Entries 8 and 9). With respect to both reaction time and diastereoselectivity, DBU was the best choice as the promoter for this diastereoselective cascade Michael/aldol reaction.

Table 1. Screening of the achiral base promoter.[a]

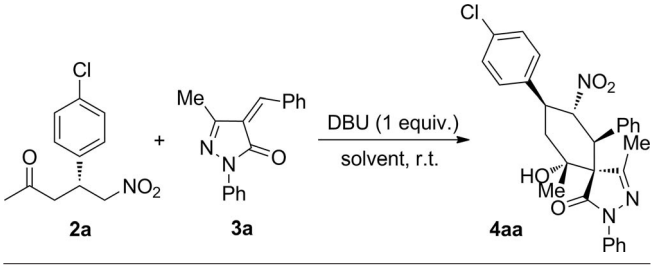


Entry	Base	Time [h]	Yield [%][b]	*dr*[c]	*ee* [%][d]
1	Et_3N	96	60	>20:1	99
2	DABCO	96	60	>20:1	>99
3	DIPEA	96	77	>20:1	>99
4	DMAP	96	72	>20:1	>99
5	TMEDA	96	80	16:1	98
6	TMG	2	58	>20:1	99
7	DBU	0.5	67	>20:1	>99
8	NaOH	24	52	>20:1	>99
9	K_2CO_3	2	50	>20:1	>99

[a] All reactions were carried out with (*R*)-4-(4-chlorophenyl)-5-nitropentan-2-one (**2a**; 0.2 mmol), (*Z*)-4-benzylidene-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**3a**; 0.2 mmol), and base (1 equiv.) in dichloromethane (1 mL) at room temperature. [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopic analysis. [d] Determined by HPLC analysis with a chiral stationary phase.

Having identified DBU as the optimal mediator for the reaction, other factors, such as solvent and base loading, that could influence the reaction were briefly investigated, and the results are summarized in Table 2. Solvent evaluation revealed that the diastereoselectivity of the reaction is sensitive to the reaction medium. Replacement of dichloromethane with other commonly used solvents, such as chloroform, ether, tetrahydrofuran (THF), toluene, ethanol, ethyl acetate, and acetonitrile, all resulted in obvious erosion in stereoselectivity (Table 2, Entries 2–8 versus Entry 1). In addition, adjustment of the base loading to 50 mol-% led to a prolonged reaction time and a marked decrease in diastereoselectivity (Table 2, Entry 9).

Table 2. Optimization of the reaction conditions.[a]



Entry	Solvent	Time [h]	Yield [%][b]	*dr* (%)[c]	*ee* [%][d]
1	CH_2Cl_2	0.5	67	>20:1	>99
2	Et_2O	0.5	62	16:1	>99
3	THF	0.5	52	12:1	>99
4	$PhCH_3$	0.5	72	12:1	>99
5	$CHCl_3$	0.5	50	9:1	>99
6	EtOH	0.5	56	9:1	>99
7	EtOAc	0.5	63	8:1	>99
8	CH_3CN	0.5	52	7:1	>99
9[e]	CH_2Cl_2	24	67	12:1	>99

[a] Unless otherwise specified, all reactions were carried out with **2a** (0.2 mmol), **3a** (0.2 mmol), and base (1 equiv.) in solvent (1 mL) at room temperature. [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by HPLC analysis with a chiral stationary phase. [e] In the presence of 50 mol-% DBU.

With the optimized reaction conditions in hand, we then investigated the scope and limitations of this diastereoselective cascade Michael/aldol reaction (Table 3). For the unsaturated pyrazolones, it appears that the position and the electronic properties of the substituents on the aromatic rings have a very limited impact on the diastereoselectivity of the reaction. The reactions of unsaturated pyrazolones that bear either electron-donating or electron-withdrawing groups with (*R*)-4-(4-chloro-

phenyl)-5-nitropentan-2-one (**2a**) all proceeded smoothly to give structurally diverse spiro-pyrazolones **4** with high levels of diastereoselectivity (Table 3, Entries 2–14; 9:1→20:1). The reaction was also applicable to unsaturated pyrazolone **3o** that contained a heteroaromatic group, which provides the desired annulation product **4ao** in good yield and excellent stereoselectivity (Table 3, Entry 15). In addition, 3-propyl-substituted unsaturated pyrazolone **3p** was tolerated well to deliver corresponding product **4ap** with >20:1 *dr* and >99 % *ee* albeit with slightly decreased yield and prolonged reaction time (Table 3, Entry 16). To further expand the scope of this methodology, we subsequently investigated the cascade Michael/aldol reactions of various optically active 4-substituted-5-nitropentan-2-ones **2** and unsaturated pyrazolone **3a** (Table 3, Entries 17–22). The reaction appears quite general with respect to other 4-substituted-5-nitropentan-2-ones that bear either an electron-donating or electron-withdrawing substituent on the benzene ring. In all cases, the reactions ran efficiently to give the desired adducts in good yields with excellent diastereo- and enantioselectivities (Table 3, Entries 17–21). Moreover, 5-nitropentan-2-one, which bears a 2-furyl group, was also proven to be a suitable reaction partner with **3a**, to deliver desired adducts **4ga** in 60 % yield with >20:1 *dr* and >99 % *ee* (Table 3, Entry 22).

The relative and absolute configuration of product **4ac** was unequivocally established by X-ray analysis (Figure 2), and the remaining configurations are deduced by analogy.[15]

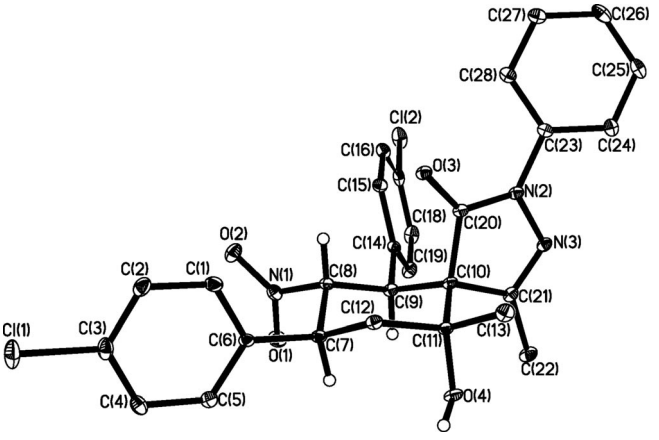
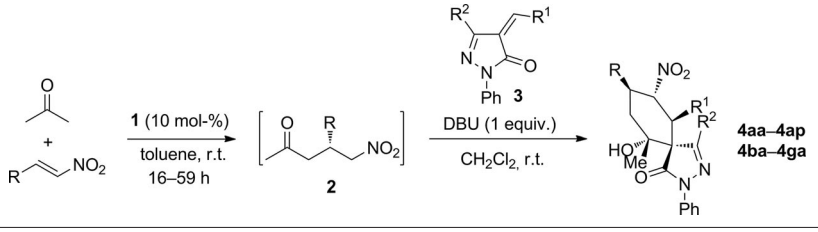


Figure 2. X-ray crystal structure of (5*S*,6*R*,8*S*,9*S*,10*S*)-**4ac**. Most of the hydrogen atoms and uncoordinated solvent have been omitted for clarity.

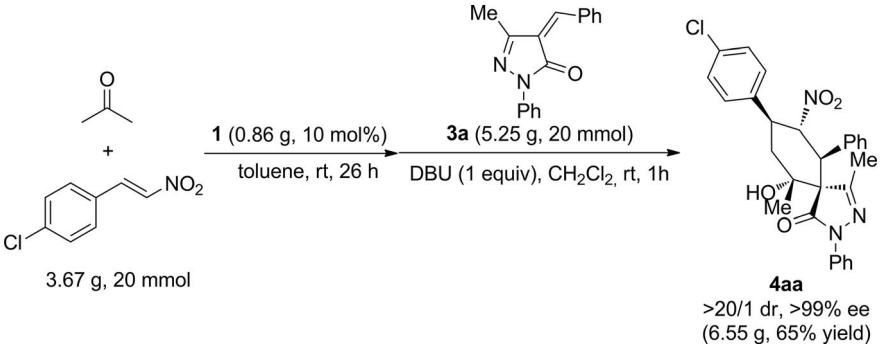
To prove the practicality of this diastereoselective cascade Michael/aldol process, a gram-scale synthesis of **4aa** was per-

Table 3. Substrate scope of the cascade Michael/aldol reaction.[a]



Entry	**4** (R, R^1, R^2)	Time [h]	Yield [%][b]	*dr*[c]	*ee* [%][d]
1	**4aa** (4-ClC_6H_4, Ph, Me)	0.5	67	>20:1	>99
2	**4ab** (4-ClC_6H_4, 4-FC_6H_4, Me)	0.1	60	>20:1	99
3	**4ac** (4-ClC_6H_4, 4-ClC_6H_4, Me)	0.1	67	>20:1	>99
4	**4ad** (4-ClC_6H_4, 3-ClC_6H_4, Me)	0.1	60	>20:1	>99
5	**4ae** (4-ClC_6H_4, 2-ClC_6H_4, Me)	0.5	56	12:1	>99
6	**4af** (4-ClC_6H_4, 2,4-$Cl_2C_6H_3$, Me)	12	42	>20:1	>99
7	**4ag** (4-ClC_6H_4, 4-BrC_6H_4, Me)	3	53	>20:1	>99
8	**4ah** (4-ClC_6H_4, 3-BrC_6H_4, Me)	3	67	9:1	>99
9	**4ai** (4-ClC_6H_4, 2-BrC_6H_4, Me)	5	50	>20:1	>99
10	**4aj** (4-ClC_6H_4, 2-$CF_3C_6H_4$, Me)	12	54	>20:1	>99
11	**4ak** (4-ClC_6H_4, 4-MeC_6H_4, Me)	6	65	>20:1	>99
12	**4al** (4-ClC_6H_4, 2-MeC_6H_4, Me)	0.1	46	>20:1	>99
13	**4am** (4-ClC_6H_4, 4-$MeOC_6H_4$, Me)	0.1	54	>20:1	>99
14	**4an** (4-ClC_6H_4, 2-$MeOC_6H_4$, Me)	0.1	62	>20:1	>99
15	**4ao** (4-ClC_6H_4, 2-Thienyl, Me)	3	62	>20:1	>99
16	**4ap** (4-ClC_6H_4, Ph, Pr)	24	48	>20:1	>99
17	**4ba** (Ph, Ph, Me)	0.1	60	>20:1	>99
18	**4ca** (4-FC_6H_4, Ph, Me)	0.1	58	>20:1	>99
19	**4da** (4-BrC_6H_4, Ph, Me)	0.1	52	>20:1	>99
20	**4ea** (4-$NO_2C_6H_4$, Ph, Me)	0.1	51	>20:1	>99
21	**4fa** (2-$MeOC_6H_4$, Ph, Me)	0.5	65	>20:1	>99
22	**4ga** (2-Furyl, Ph, Me)	0.5	60	>20:1	>99

[a] Unless otherwise specified, all reactions were carried out with **2a** (0.2 mmol, crude product prepared from **1**-catalyzed asymmetric Michael addition of acetone to nitroolefin), **3a** (0.2 mmol), and base (1 equiv.) in dichloromethane (1 mL) at room temperature. [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopic analysis. [d] Determined by HPLC analysis with a chiral stationary phase.



Scheme 2. Gram-scale synthesis of spiro-pyrazolone **4aa**.

formed. The result is shown in Scheme 2. When crude (*R*)-4-(4-chlorophenyl)-5-nitropentan-2-one (**2a**) was obtained by reaction of 1-chloro-4-[(*E*)-2-nitrovinyl]benzene (3.67 g) with acetone in the presence of catalyst **1** (0.86 g), (*Z*)-4-benzylidene-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**3a**) (5.25 g; 20 mmol) were loaded, spiro-pyrazolone **4aa** (6.55 g) was obtained (65 % yield) without any erosion in the stereochemical outcome of the reaction.

To account for the observed high diastereoselectivity, a plausible chair-like transition state is proposed, which explains the stereocontrol and specificity of the reaction (Figure 3). The stereochemistry comes from a chair arrangement in the conformation of the transition state. The phenyl group prefers to be equatorial in the transition state and directs the formation of the four new chiral centers.

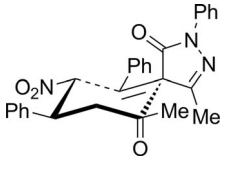


Figure 3. Proposed transition state.

Conclusions

In conclusion, we have uncovered that readily available optically active 4-substituted 5-nitropentan-2-ones are excellent chiral building blocks for the stereocontrolled construction of potentially biologically important spiro-pyrazolone scaffolds. A variety of spirocyclohexanepyrazolone derivatives that bear two quaternary and three tertiary stereocenters were obtained in good yields and excellent diastereoselectivities through DBU-promoted cascade Michael/aldol reactions between 4-substituted 5-nitropentan-2-ones and unsaturated pyrazolones. Moreover, the reaction can be scaled up without any loss in reaction efficiency in terms of yield and diastereoselectivity. This method is a simple and practical process, which features mild reaction conditions, readily available starting materials, and broad substrate scope, for the stereocontrolled construction of spiro-pyrazolone scaffolds with two quaternary and three tertiary stereocenters in a highly diastereo- and enantioselective manner.

Experimental Section

General Methods: Unless otherwise stated, all reagents were purchased from commercial suppliers and used as received. All reactions were carried out in air, without distillation of solvents, and without any precautions to exclude moisture unless otherwise mentioned. NMR spectra were acquired with a Varian 400 MHz instrument. Chemical shifts are measured relative to residual solvent peaks as an internal standard set to δ = 7.26 and 77.0 ($CDCl_3$) ppm. HRMS spectra were recorded with a Varian QFT-ESI instrument. Specific rotations were measured with a Perkin–Elmer 341MC polarimeter. Enantiomeric excesses were determined with a Shimadzu LC-20AT or a HP-1100 instrument (chiral column; mobile phase: hexane/*i*PrOH). Melting points were determined with a Taike X-4 melting point apparatus.

General Procedure for the Diastereoselective Cascade Michael/Aldol Reactions: A mixture of thiophosphinamide catalyst **1** (8.6 mg, 0.02 mmol) and acetone (0.6 mmol, 3 equiv.) in toluene (0.5 mL) was stirred at room temperature until a clear solution formed. Then, to the resulting solution was added nitroolefin (0.2 mmol) at the same temperature. After the reaction is complete (monitored by TLC), the reaction mixture was concentrated under reduced pressure to afford crude 4-substituted 5-nitropentan-2-ones **2**, which were used directly in the following DBU-promoted cascade Michael/aldol reactions.

To a solution of crude 4-substituted 5-nitropentan-2-ones **2** and unsaturated pyrazolones **3** (0.2 mmol) in dichloromethane (1 mL) was added DBU (29.8 µL, 0.2 mmol) in one portion at room temperature, and the resulting mixture was stirred at the same temperature until the reaction was complete (monitored by TLC). After removal of the solvent, the crude product was purified by column chromatography on silica gel (200–300 mesh, petroleum ether/ethyl acetate = 8:1) to afford desired spiro-pyrazolones **4**. The title compounds were fully characterized by ^1H and ^{13}C NMR spectroscopy, HRMS, and specific rotation. The enantiomeric excess of the pure products was determined by HPLC analysis with a chiral stationary phase.

(5*S*,6*R*,8*S*,9*S*,10*S*)-8-(4-Chlorophenyl)-6-hydroxy-4,6-dimethyl-9-nitro-2,10-diphenyl-2,3-diazaspiro[4.5]dec-3-en-1-one (4aa): Yellow solid, 67 % yield, m.p. 105–108 °C. $[\alpha]_D^{20}$ = +49.6 (*c* = 1.0, $CHCl_3$). >20:1 *dr*, >99 % *ee* for the major diastereomer. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 7.6 Hz, 2 H), 7.40 (t, *J* = 8.0 Hz, 2 H), 7.36 (d, *J* = 8.4 Hz, 2 H), 7.31 (d, *J* = 8.4 Hz, 2 H), 7.16–7.26 (m, 6 H), 5.99 (t, *J* = 11.6 Hz, 1 H), 4.29 (d, *J* = 12.0 Hz, 1 H), 3.84 (ddd, *J* = 13.2, 11.6, 4.4 Hz, 1 H), 3.13 (t, *J* = 13.6 Hz, 1 H), 2.26 (s, 3 H), 1.74 (dd, *J* = 14.4, 4.4 Hz, 1 H), 1.67 (s, 1 H), 1.23 (s, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 172.6, 160.78 137.7, 137.0, 133.7, 133.2,

129.2, 129.0, 128.9 (2 C), 126.0, 119.9, 90.1, 72.3, 65.9, 46.8, 43.2, 40.9, 26.0, 17.4 ppm. HRMS (ESI): *m/z* calcd. for $C_{28}H_{27}ClN_3O_4$ [M + H]$^+$: 504.1685; found 504.1687. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol, 98:2, flow rate: 1.0 mL/min, wavelength: 220 nm): R_t = 95.22 min (major, major diastereomer).

(5*S*,6*R*,8*S*,9*S*,10*S*)-8-(4-Chlorophenyl)-10-(4-fluorophenyl)-6-hydroxy-4,6-dimethyl-9-nitro-2-phenyl-2,3-diazaspiro[4.5]dec-3-en-1-one (4ab): Yellow solid, 60 % yield, m.p. 126–130 °C. $[\alpha]_D^{20}$ = +45.2 (*c* = 1.0, $CHCl_3$), >20:1 *dr*, 99 % *ee* for the major diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 7.6 Hz, 2 H), 7.41 (t, *J* = 8.0 Hz, 2 H), 7.35 (d, *J* = 8.8 Hz, 2 H), 7.31 (d, *J* = 8.8 Hz, 2 H), 7.21–7.26 (m, 3 H), 6.86 (t, *J* = 8.0 Hz, 2 H), 5.94 (t, *J* = 11.6 Hz, 1 H), 4.29 (d, *J* = 11.6 Hz, 1 H), 3.80–3.87 (m, 1 H), 3.12 (t, *J* = 13.2 Hz, 1 H), 2.25 (s, 3 H), 1.78 (dd, *J* = 14.4, 4.4 Hz, 1 H), 1.66 (s, 1 H), 1.24 (s, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 172.4, 162.7 (d, *J* = 245.6 Hz), 160.7, 137.5, 136.9, 133.8, 129.2, 129.1 (d, *J* = 3.4 Hz), 129.0, 128.8, 128.7 (d, *J* = 6.6 Hz), 126.1, 119.7, 116.0 (d, *J* = 21.4 Hz), 90.2, 72.3, 65.9, 46.0, 43.1, 40.8, 26.0, 17.4 ppm. HRMS (ESI): *m/z* calcd. for $C_{28}H_{26}ClFN_3O_4$ [M + H]$^+$ 522.1590; found 522.1600. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol, 98:2, flow rate: 0.8 mL/min, wavelength: 220 nm): R_t = 43.84 (major, minor diastereomer), 61.72 (major, major diastereomer) and 104.14 min (minor, major diastereomer).

(5*S*,6*R*,8*S*,9*S*,10*S*)-8,10-Bis(4-chlorophenyl)-6-hydroxy-4,6-dimethyl-9-nitro-2-phenyl-2,3-diazaspiro[4.5]dec-3-en-1-one (4ac): Yellow solid, 67 % yield, m.p. 123–125 °C. $[\alpha]_D^{20}$ = +103.6 (*c* = 1.0, $CHCl_3$). >20:1 *dr*, >99 % *ee* for the major diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 (d, *J* = 7.6 Hz, 2 H), 7.42 (t, *J* = 7.6 Hz, 2 H), 7.31–7.36 (m, 4 H), 7.23–7.27 (m, 1 H), 7.16 (s, 4 H), 5.94 (t, *J* = 11.6 Hz, 1 H), 4.28 (d, *J* = 11.6 Hz, 1 H), 3.80–3.87 (m, 1 H), 3.11 (t, *J* = 13.2 Hz, 1 H), 2.25 (s, 3 H), 1.78 (dd, *J* = 14.4, 3.2 Hz, 1 H), 1.69 (s, 1 H), 1.23 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.3, 160.6, 137.5, 136.8, 134.9, 133.8, 131.8, 129.2 (2 C), 129.0 (2 C), 126.1, 119.7 (2 C), 90.0, 72.3, 65.8, 46.1, 43.1, 40.8, 26.0, 17.4 ppm. HRMS (ESI): *m/z* calcd. for $C_{28}H_{26}Cl_2N_3O_4$ [M + H]$^+$ 538.1295; found 538.1288. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol, 88:12, flow rate: 1.0 mL/min, wavelength: 220 nm): R_t = 5.92 (major, major diastereomer), 9.53 (minor, major diastereomer), 11.05 (major, minor diastereomer) and 12.60 min (minor, minor diastereomer).

(5*S*,6*R*,8*S*,9*S*,10*S*)-10-(3-Chlorophenyl)-8-(4-chlorophenyl)-6-hydroxy-4,6-dimethyl-9-nitro-2-phenyl-2,3-diazaspiro[4.5]dec-3-en-1-one (4ad): White solid, 60 % yield, m.p. 109–112 °C. $[\alpha]_D^{20}$ = +59.6 (*c* = 1.0, $CHCl_3$). >20:1 *dr*, >99 % *ee* for the major diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 7.6 Hz, 2 H), 7.41 (t, *J* = 8.0 Hz, 2 H), 7.31–7.34 (m, 4 H), 7.21–7.27 (m, 3 H), 6.87 (t, *J* = 8.0 Hz, 2 H), 5.94 (t, *J* = 11.6 Hz, 1 H), 4.29 (d, *J* = 11.6 Hz, 1 H), 3.83 (dt, *J* = 12.8, 4.0 Hz, 1 H), 3.12 (t, *J* = 13.2 Hz, 1 H), 2.25 (s, 3 H), 1.78 (dd, *J* = 14.4, 4.4 Hz, 1 H), 1.66 (s, 1 H), 1.24 (s, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 172.3, 160.5, 137.5, 136.7, 135.3, 134.7, 133.9, 130.2, 129.2 (2 C), 129.0, 128.9, 126.2, 120.1, 89.9, 72.3, 65.7, 46.4, 43.1, 40.8, 25.9, 17.4 ppm. HRMS (ESI): *m/z* calcd. for $C_{28}H_{26}Cl_2N_3O_4$ [M + H]$^+$ 538.1295; found 538.1297. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol, 98:2, flow rate: 1.0 mL/min, wavelength: 220 nm): R_t = 81.30 min (major, major diastereomer).

(5*S*,6*R*,8*S*,9*S*,10*R*)-10-(2-Chlorophenyl)-8-(4-chlorophenyl)-6-hydroxy-4,6-dimethyl-9-nitro-2-phenyl-2,3-diazaspiro[4.5]dec-3-en-1-one (4ae): Yellow solid, 56 % yield, m.p. 89–92 °C. $[\alpha]_D^{20}$ = +59.6 (*c* = 1.0, $CHCl_3$). 12:1 *dr*, >99 % *ee* for the major diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 (d, *J* = 7.6 Hz, 2 H), 7.30–7.44 (m, 8 H), 7.25 (t, *J* = 7.6 Hz, 1 H), 7.12 (dt, *J* = 7.6, 1.6 Hz, 1 H), 7.02 (dt, *J* = 7.6, 1.2 Hz, 1 H), 5.95 (t, *J* = 11.6 Hz, 1 H), 5.22 (d, *J* = 11.6 Hz, 1 H), 3.92 (ddd, *J* = 13.2, 11.6, 4.8 Hz, 1 H), 3.14 (dd, *J* = 14.4, 13.6 Hz, 1 H), 2.36 (s, 3 H), 1.80 (dd, *J* = 14.4, 4.4 Hz, 1 H), 1.76 (s, 1 H), 1.24 (s, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 172.6, 161.2, 137.6, 137.0, 134.3, 133.8, 131.5, 130.7, 129.9, 129.2, 129.0 (2 C), 128.1, 127.4, 126.1, 119.8, 90.0, 72.5, 66.1, 43.2, 41.2, 40.9, 25.8, 17.3 ppm. HRMS (ESI): *m/z* calcd. for $C_{28}H_{26}Cl_2N_3O_4$ [M + H]$^+$ 538.1295; found 538.1288. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol, 98:2, flow rate: 1.0 mL/min, wavelength: 220 nm): R_t = 34.25 (major, minor diastereomer), 51.47 (major, major diastereomer) and 67.21 min (minor, minor diastereomer).

(5*S*,6*R*,8*S*,9*S*,10*R*)-8-(4-Chlorophenyl)-10-(2,4-dichlorophenyl)-6-hydroxy-4,6-dimethyl-9-nitro-2-phenyl-2,3-diazaspiro[4.5]dec-3-en-1-one (4af): Pale yellow solid, 42 % yield, m.p. 117–122 °C. $[\alpha]_D^{20}$ = +79.2 (*c* = 1.0, $CHCl_3$). >20:1 *dr*, >99 % *ee* for the major diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 8.4 Hz, 2 H), 7.44 (t, *J* = 8.0 Hz, 2 H), 7.29–7.36 (m, 6 H), 7.25–7.26 (m, 1 H), 7.01 (dd, *J* = 8.4, 1.6 Hz, 1 H), 5.91 (t, *J* = 11.6 Hz, 1 H), 5.16 (d, *J* = 11.6 Hz, 1 H), 3.91 (dt, *J* = 12.8, 4.4 Hz, 1 H), 3.12 (t, *J* = 14.0 Hz, 1 H), 2.35 (s, 3 H), 1.81 (dd, *J* = 14.4, 4.4 Hz, 1 H), 1.73 (s, 1 H), 1.24 (s, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 172.4, 161.0, 137.4, 136.9, 135.2, 135.1, 133.9, 130.5, 130.2, 129.2, 129.0 (2 C), 127.8, 126.2, 119.6, 89.9, 72.5, 65.9, 43.1, 40.8 (2 C), 25.8, 17.3 ppm. HRMS (ESI): *m/z* calcd. for $C_{28}H_{25}Cl_3N_3O_4$ [M + H]$^+$ 572.0905; found 572.0896. HPLC analysis (Chiralpak OD-H column, hexane/2-propanol, 98:2, flow rate: 1.0 mL/min, wavelength: 220 nm): R_t = 125.11 min (major, major diastereomer).

(5*S*,6*R*,8*S*,9*S*,10*S*)-10-(4-Bromophenyl)-8-(4-chlorophenyl)-6-hydroxy-4,6-dimethyl-9-nitro-2-phenyl-2,3-diazaspiro[4.5]dec-3-en-1-one (4ag): Yellow solid, 53 % yield, m.p. 107–110 °C. $[\alpha]_D^{20}$ = +74.8 (*c* = 1.0, $CHCl_3$). >20:1 *dr*, >99 % *ee* for the major diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 8.0 Hz, 2 H), 7.41 (t, *J* = 8.0 Hz, 2 H), 7.23–7.35 (m, 7 H), 7.09 (d, *J* = 8.0 Hz, 2 H), 5.93 (t, *J* = 11.6 Hz, 1 H), 4.26 (d, *J* = 12.0 Hz, 1 H), 3.82 (ddd, *J* = 13.2, 11.6, 4.4 Hz, 1 H), 3.08 (t, *J* = 14.4 Hz, 1 H), 2.23 (s, 3 H), 1.76 (s, 1 H), 1.74 (dd, *J* = 14.4, 4.4 Hz, 1 H), 1.19 (s, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 172.3, 160.6, 137.5, 136.8, 133.8, 132.4, 132.1, 129.2, 129.0, 128.9, 123.1, 119.7, 90.0, 72.3, 65.7, 46.2, 43.1, 40.7, 25.9, 17.4 ppm. HRMS (ESI): *m/z* calcd. for $C_{28}H_{26}BrClN_3O_4$ [M + H]$^+$ 582.0790; found 582.0792. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol, 98:2, flow rate: 1.0 mL/min, wavelength: 220 nm): R_t = 33.93 (major, minor diastereomer) and 51.39 min (major, major diastereomer).

(5*S*,6*R*,8*S*,9*S*,10*S*)-10-(3-Bromophenyl)-8-(4-chlorophenyl)-6-hydroxy-4,6-dimethyl-9-nitro-2-phenyl-2,3-diazaspiro[4.5]dec-3-en-1-one (4ah): Yellow solid, 67 % yield, m.p. 88–90 °C. $[\alpha]_D^{20}$ = +57.6 (*c* = 1.0, $CHCl_3$). 9:1 *dr*, >99 % *ee* for the major diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 8.0 Hz, 2 H), 7.16–7.43 (m, 10 H), 7.05 (t, *J* = 7.2 Hz, 1 H), 5.94 (t, *J* = 11.6 Hz, 1 H), 4.26 (d, *J* = 12.0 Hz, 1 H), 3.79–3.86 (m, 1 H), 3.10 (t, *J* = 13.2 Hz, 1 H), 2.25 (s, 3 H), 1.77 (dd, *J* = 14.4, 4.0 Hz, 1 H), 1.72 (s, 1 H), 1.23 (s, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 172.3, 160.5, 137.5, 137.3, 136.7, 135.6, 133.8, 132.1, 130.4, 129.2, 129.0, 128.9, 128.8, 126.2, 122.9, 120.1, 89.8, 72.2, 65.7, 46.3, 43.1, 40.8, 26.0, 17.4 ppm. HRMS (ESI): *m/z* calcd. for $C_{28}H_{26}BrClN_3O_4$ [M + H]$^+$ 582.0790; found 582.0790. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol, 98:2, flow rate: 1.0 mL/min, wavelength: 220 nm): R_t = 34.50 (major, minor diastereomer) and 85.16 min (major, major diastereomer).

(5*S*,6*R*,8*S*,9*S*,10*R*)-10-(2-Bromophenyl)-8-(4-chlorophenyl)-6-hydroxy-4,6-dimethyl-9-nitro-2-phenyl-2,3-diazaspiro[4.5]dec-3-en-1-one (4ai): Yellow solid, 50 % yield, m.p. 147–150 °C. $[\alpha]_D^{20}$ =

+66 (c = 1.0, $CHCl_3$). >20:1 *dr*, >99 % *ee* for the major diastereomer. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.72 (d, J = 7.6 Hz, 2 H), 7.51 (d, J = 7.2 Hz, 1 H), 7.26–7.45 (m, 8 H), 7.06 (t, J = 7.2 Hz, 2 H), 5.95 (t, J = 11.6 Hz, 1 H), 5.20 (d, J = 11.6 Hz, 1 H), 3.91–3.98 (m, 1 H), 3.14 (t, J = 14.4 Hz, 1 H), 2.40 (s, 3 H), 1.81 (dd, J = 14.4, 4.0 Hz, 1 H), 1.75 (s, 1 H), 1.24 (s, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 172.6, 161.2, 137.6, 137.0, 134.2, 133.8, 133.2, 130.2, 129.2, 129.1, 129.0, 128.2, 128.1, 126.1, 125.3, 119.8, 90.0, 72.5, 66.1, 44.0, 43.1, 40.9, 25.8, 17.8 ppm. HRMS (ESI): *m/z* calcd. for $C_{28}H_{26}BrClN_3O_4$ $[M + H]^+$ 582.0790; found 582.0782. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol, 98:2, flow rate: 1.0 mL/min, wavelength: 220 nm): R_t = 61.35 min (major, major diastereomer).

(5*S*,6*R*,8*S*,9*S*,10*S*)-8-(4-Chlorophenyl)-6-hydroxy-4,6-dimethyl-9-nitro-2-phenyl-10-[2-(trifluoromethyl)phenyl]-2,3-diazaspiro-[4.5]dec-3-en-1-one (4aj): Pale yellow solid, 54 % yield, m.p. 116–119 °C. $[\alpha]_D^{20}$ = +54.4 (c = 1.0, $CHCl_3$). >20:1 *dr*, >99 % *ee* for the major diastereomer. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.73 (d, J = 7.6 Hz, 2 H), 7.63 (d, J = 7.6 Hz, 1 H), 7.60 (dd, J = 8.0, 0.8 Hz, 1 H), 7.44 (t, J = 8.0 Hz, 2 H), 7.39 (d, J = 8.4 Hz, 2 H), 7.26–7.35 (m, 5 H), 6.08 (t, J = 11.6 Hz, 1 H), 5.17 (d, J = 11.6 Hz, 1 H), 3.95 (ddd, J = 12.6, 11.2, 4.4 Hz, 1 H), 3.14 (dd, J = 14.4, 13.2 Hz, 1 H), 2.21 (s, 3 H), 1.81 (dd, J = 14.4, 4.8 Hz, 1 H), 1.73 (s, 1 H), 1.23 (s, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 172.1, 160.4, 137.4, 136.7, 134.5, 133.9, 129.5, 129.2, 129.0, 128.9, 126.2, 125.9, 119.7, 89.7, 72.3, 65.8, 46.5, 43.1, 40.8, 25.9, 17.4 ppm. HRMS (ESI): *m/z* calcd. for $C_{29}H_{26}ClF_3N_3O_4$ $[M + H]^+$ 572.1558; found 572.1563. HPLC analysis (Chiralpak OD-H column, hexane/2-propanol, 98:2, flow rate: 1.0 mL/min, wavelength: 220 nm): R_t = 102.62 min (major, major diastereomer).

(5*S*,6*R*,8*S*,9*S*,10*S*)-8-(4-Chlorophenyl)-6-hydroxy-4,6-dimethyl-9-nitro-2-phenyl-10-(*p*-tolyl)-2,3-diazaspiro[4.5]dec-3-en-1-one (4ak): Yellow solid, 65 % yield, m.p. 114–117 °C. $[\alpha]_D^{20}$ = +78 (c = 1.0, $CHCl_3$). >20:1 *dr*, >99 % *ee* for the major diastereomer. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.68 (dd, J = 8.4 Hz, 2 H), 7.41 (t, J = 7.6 Hz, 2 H), 7.35 (d, J = 8.4 Hz, 2 H), 7.31 (d, J = 8.4 Hz, 2 H), 7.24 (t, J = 7.2 Hz, 1 H), 7.09 (br. s, 2 H), 6.95 (d, J = 7.6 Hz, 2 H), 5.97 (t, J = 11.6 Hz, 1 H), 4.25 (d, J = 12.0 Hz, 1 H), 3.83 (dt, J = 12.0, 4.0 Hz, 1 H), 3.10 (t, J = 13.6 Hz, 1 H), 2.25 (s, 3 H), 2.20 (s, 3 H), 1.75 (dd, J = 13.6, 3.6 Hz, 1 H), 1.73 (s, 1 H), 1.20 (s, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 172.7, 161.0, 138.6, 137.8, 137.0, 133.7, 130.1, 129.6, 129.1, 129.0, 128.9, 126.0, 119.9, 90.3, 72.2, 66.0, 46.4, 43.2, 40.8, 25.9, 21.0, 17.4 ppm. HRMS (ESI): *m/z* calcd. for $C_{29}H_{29}ClN_3O_4$ $[M + H]^+$ 518.1841; found 518.1843. HPLC analysis (Chiralpak OD-H column, hexane/2-propanol, 95:5, flow rate: 1.0 mL/min, wavelength: 220 nm): R_t = 20.24 (minor, major diastereomer) and 26.28 min (major, major diastereomer).

(5*S*,6*R*,8*S*,9*S*,10*S*)-8-(4-Chlorophenyl)-6-hydroxy-4,6-dimethyl-9-nitro-2-phenyl-10-(*o*-tolyl)-2,3-diazaspiro[4.5]dec-3-en-1-one (4al): Yellow solid, 46 % yield, m.p. 95–98 °C. $[\alpha]_D^{20}$ = +54.8 (c = 1.0, $CHCl_3$). >20:1 *dr*, 98 % *ee* for major diastereomer. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, J = 8.0 Hz, 2 H), 7.45 (t, J = 7.6 Hz, 2 H), 7.39 (d, J = 8.0 Hz, 2 H), 7.32 (d, J = 8.4 Hz, 2 H), 7.26–7.31 (m, 2 H), 7.06–7.11 (m, 2 H), 6.95 (t, J = 7.2 Hz, 1 H), 6.01 (t, J = 11.2 Hz, 1 H), 4.83 (d, J = 11.6 Hz, 1 H), 3.88 (dt, J = 12.0, 4.0 Hz, 1 H), 3.15 (t, J = 14.0 Hz, 1 H), 2.47 (s, 3 H), 2.23 (s, 3 H), 1.82 (s, 1 H), 1.78 (dd, J = 14.4, 4.4 Hz, 1 H), 1.23 (s, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 173.1, 160.7, 137.8, 137.1, 136.4, 133.7, 132.0, 131.6, 129.1, 129.0, 128.9, 128.4, 126.6, 126.3, 126.0, 119.9, 90.5, 72.7, 66.2, 43.6, 41.1, 40.9, 25.9, 19.6, 17.0 ppm. HRMS (ESI): *m/z* calcd. for $C_{29}H_{29}ClN_3O_4$ $[M + H]^+$ 518.1841; found 518.1849. HPLC analysis (Chiralpak OD-H column, hexane/2-propanol, 95:5, flow rate: 1.0 mL/min, wavelength: 220 nm): R_t = 20.14 (minor, major diastereomer) and 31.56 min (major, major diastereomer).

(5*S*,6*R*,8*S*,9*S*,10*S*)-8-(4-Chlorophenyl)-6-hydroxy-10-(4-methoxyphenyl)-4,6-dimethyl-9-nitro-2-phenyl-2,3-diazaspiro[4.5]dec-3-en-1-one (4am): Yellow solid, 54 % yield, m.p. 93–96 °C. $[\alpha]_D^{20}$ = +65.2 (c = 1.0, $CHCl_3$). >20:1 *dr*, >99 % *ee* for the major diastereomer. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.68 (d, J = 8.4 Hz, 2 H), 7.40 (t, J = 8.0 Hz, 2 H), 7.35 (d, J = 8.4 Hz, 2 H), 7.31 (d, J = 8.4 Hz, 2 H), 7.23 (t, J = 7.6 Hz, 1 H), 7.13 (d, J = 7.6 Hz, 2 H), 6.67 (d, J = 8.8 Hz, 2 H), 5.94 (t, J = 11.6 Hz, 1 H), 4.23 (d, J = 12.0 Hz, 1 H), 3.83 (ddd, J = 3.2, 11.6, 4.4 Hz, 1 H), 3.68 (s, 3 H), 3.10 (dd, J = 14.4, 13.6 Hz, 1 H), 2.24 (s, 3 H), 1.75 (dd, J = 14.4, 4.4 Hz, 1 H), 1.70 (s, 1 H), 1.21 (s, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 172.7, 160.9, 159.7, 137.8, 137.1, 133.7, 129.2 129.0, 128.9, 126.0, 125.1, 119.8, 114.3, 90.4, 72.3, 66.1, 55.1, 46.1, 43.2, 40.9, 26.0, 17.4 ppm. HRMS (ESI): *m/z* calcd. for $C_{29}H_{29}ClN_3O_5$ $[M + H]^+$ 534.1790; found 534.1798. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol, 97:3, flow rate: 1.0 mL/min, wavelength: 220 nm): R_t = 27.48 (major, minor diastereomer) and 52.76 min (major, major diastereomer).

(5*S*,6*R*,8*S*,9*S*,10*S*)-8-(4-Chlorophenyl)-6-hydroxy-10-(2-methoxyphenyl)-4,6-dimethyl-9-nitro-2-phenyl-2,3-diazaspiro[4.5]dec-3-en-1-one (4an): Yellow solid, 62 % yield, m.p. 171–174 °C. $[\alpha]_D^{20}$ = +48.8 (c = 1.0, $CHCl_3$). >20:1 *dr*, >99 % *ee* for the major diastereomer. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, J = 7.6 Hz, 2 H), 7.39 (t, J = 7.6 Hz, 2 H), 7.29–7.37 (m, 5 H), 7.22 (t, J = 7.6 Hz, 1 H), 7.13 (dt, J = 8.0, 1.6 Hz, 1 H), 6.80 (d, J = 8.0 Hz, 1 H), 6.71 (t, J = 7.6 Hz, 1 H), 5.94 (t, J = 11.6 Hz, 1 H), 5.16 (d, J = 12.0 Hz, 1 H), 3.87 (dt, J = 12.4, 4.4 Hz, 1 H), 3.84 (s, 3 H), 3.14 (t, J = 14.0 Hz, 1 H), 2.28 (s, 3 H), 1.78 (dd, J = 14.4, 4.4 Hz, 1 H), 1.73 (s, 1 H), 1.22 (s, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 173.0, 161.6, 156.8, 137.9, 137.0, 133.6, 129.7, 129.1, 129.0, 128.8, 127.6, 125.9, 121.7, 120.9, 120.0, 111.4, 90.2, 72.3, 66.3, 55.6, 43.3, 41.0, 36.8, 25.9, 16.7 ppm. HRMS (ESI): *m/z* calcd. for $C_{29}H_{29}ClN_3O_5$ $[M + H]^+$ 534.1790; found 534.1794. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol, 97:3, flow rate: 1.0 mL/min, wavelength: 220 nm): R_t = 28.07 (major, minor diastereomer) and 45.190 min (major, major diastereomer).

(5*S*,6*R*,8*S*,9*S*,10*S*)-8-(4-Chlorophenyl)-6-hydroxy-4,6-dimethyl-9-nitro-2-phenyl-10-(thiophen-2-yl)-2,3-diazaspiro[4.5]dec-3-en-1-one (4ao): Yellow solid, 62 % yield, m.p. 173–175 °C. $[\alpha]_D^{20}$ = +65.2 (c = 1.0, $CHCl_3$). >20:1 *dr*, >99 % *ee* for the major diastereomer. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.75 (dd, J = 8.4, 1.2 Hz, 2 H), 7.42 (t, J = 7.6 Hz, 2 H), 7.30–7.34 (m, 4 H), 7.24 (t, J = 7.6 Hz, 1 H), 7.10 (d, J = 5.2 Hz, 1 H), 6.91 (dd, J = 3.6, 1.2 Hz, 1 H), 6.79 (dd, J = 4.8, 3.6 Hz, 1 H), 5.91 (t, J = 11.6 Hz, 1 H), 4.61 (d, J = 11.2 Hz, 1 H), 3.81 (ddd, J = 13.2, 11.6, 4.4 Hz, 1 H), 3.04 (dd, J = 14.4, 13.6 Hz, 1 H), 2.28 (s, 3 H), 1.80 (s, 1 H), 1.73 (dd, J = 14.4, 4.4 Hz, 1 H), 1.22 (s, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 172.2, 160.8, 137.5, 137.1, 135.1, 133.8, 129.2, 129.0, 128.9, 127.2, 127.0, 126.0, 125.9, 119.7, 91.4, 72.3, 66.2, 43.1, 41.9, 40.6, 26.0, 17.3 ppm. HRMS (ESI): *m/z* calcd. for $C_{26}H_{25}ClN_3O_4S$ $[M + H]^+$ 510.1249; found 510.1253. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol, 98:2, flow rate: 1.0 mL/min, wavelength: 220 nm): R_t = 34.13 (major, minor diastereomer), 43.11 (minor, minor diastereomer), 76.68 (minor, major diastereomer) and 112.23 min (major, major diastereomer).

(5*S*,6*R*,8*S*,9*S*,10*S*)-8-(4-Chlorophenyl)-6-hydroxy-6-methyl-9-nitro-2,10-diphenyl-4-propyl-2,3-diazaspiro[4.5]dec-3-en-1-one (4ap): Yellow solid, 48 % yield, m.p. 170–173 °C. $[\alpha]_D^{20}$ = +51.6 (c = 1.0, $CHCl_3$). >20:1 *dr*, >99 % *ee* for the major diastereomer. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, J = 8.0 Hz, 2 H), 7.40 (t, J = 7.6 Hz, 2 H), 7.36 (d, J = 8.4 Hz, 2 H), 7.31 (d, J = 8.4 Hz, 2 H), 7.16–7.26 (m, 6 H), 5.98 (t, J = 11.6 Hz, 1 H), 4.29 (d, J = 11.6 Hz, 1 H), 3.84 (dt, J = 11.6, 4.0 Hz, 1 H), 3.13 (t, J = 14.4 Hz, 1 H), 2.63–2.72 (m, 1 H), 2.43–2.51 (m, 1 H), 1.76 (dd, J = 14.4, 4.4 Hz, 1 H), 1.67–1.74 (m, 1 H), 1.66 (s, 1 H), 1.38–1.47 (m, 1 H), 1.22 (s, 3 H), 0.93 (t, J = 7.6 Hz,

3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 172.7, 163.4, 137.8, 137.2, 133.7, 133.3, 129.2, 129.0, 128.9, 128.8, 125.9, 119.8, 90.2, 72.4, 66.1, 47.0, 43.2, 41.0, 32.8, 26.1, 18.4, 13.9 ppm. HRMS (ESI): *m/z* calcd. for $C_{30}H_{31}ClN_3O_4$ $[M + H]^+$ 532.1998; found 532.2001. HPLC analysis (Chiralpak OD-H column, hexane/2-propanol, 95:5, flow rate: 1.0 mL/min, wavelength: 220 nm): R_t = 15.91 (minor, major diastereomer) and 19.98 (major, major diastereomer).

(5*S*,6*R*,8*S*,9*S*,10*S*)-6-Hydroxy-4,6-dimethyl-9-nitro-2,8,10-triphenyl-2,3-diazaspiro[4.5]dec-3-en-1-one (4ba): Pale yellow solid, 60 % yield, m.p. 167–170 °C. $[\alpha]_D^{20}$ = +63.2 (*c* = 1.0, $CHCl_3$). >20:1 *dr*, >99 % *ee* for the major diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 8.0 Hz, 2 H), 7.33–7.43 (m, 6 H), 7.21–7.29 (m, 4 H), 7.15–7.17 (m, 2 H), 6.04 (t, *J* = 11.6 Hz, 1 H), 4.31 (d, *J* = 11.6 Hz, 1 H), 3.85 (dt, *J* = 12.0, 4.0 Hz, 1 H), 3.18 (t, *J* = 14.0 Hz, 1 H), 2.27 (s, 3 H), 1.80 (dd, *J* = 14.4, 4.0 Hz, 1 H), 1.70 (s, 1 H), 1.23 (s, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 172.6, 160.9, 139.2, 137.0, 133.4, 129.1, 129.0, 128.9, 128.8 (2 C), 127.9, 127.6, 127.3, 125.9, 119.9, 90.2, 72.4, 66.0, 46.9, 43.8, 41.1, 26.0, 17.5 ppm. HRMS (ESI): *m/z* calcd. for $C_{28}H_{28}N_3O_4$ $[M + H]^+$ 470.2074; found 470.2078. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol, 98:2, flow rate: 1.0 mL/min, wavelength: 220 nm): R_t = 133.02 min (major, major diastereomer).

(5*S*,6*R*,8*S*,9*S*,10*S*)-8-(4-Fluorophenyl)-6-hydroxy-4,6-dimethyl-9-nitro-2,10-diphenyl-2,3-diazaspiro[4.5]dec-3-en-1-one (4ca): Pale yellow solid, 58 % yield, m.p. 184–187 °C. $[\alpha]_D^{20}$ = +74 (*c* = 1.0, $CHCl_3$). >20:1 *dr*, >99 % *ee* for the major diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 8.0 Hz, 2 H), 7.37–7.42 (m, 4 H), 7.14–7.26 (m, 6 H), 7.03 (t, *J* = 8.4 Hz, 2 H), 5.99 (t, *J* = 11.6 Hz, 1 H), 4.29 (d, *J* = 11.6 Hz, 1 H), 3.84 (ddd, *J* = 13.2, 11.6, 4.4 Hz, 1 H), 3.13 (t, *J* = 14.0 Hz, 1 H), 2.25 (s, 3 H), 1.76 (dd, *J* = 14.4, 4.4 Hz, 1 H), 1.74 (s, 1 H), 1.21 (s, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 172.6, 162.3 (d, *J* = 246.4 Hz), 160.8, 137.0, 135.0 (d, *J* = 3.1 Hz), 133.2, 129.2 (d, *J* = 8.1 Hz), 128.9 (2 C), 128.8, 126.0, 119.9, 115.9 (d, *J* = 21.3 Hz), 90.4, 72.3, 65.9, 46.8, 43.0, 41.1, 26.0, 17.4 ppm. HRMS (ESI): *m/z* calcd. for $C_{28}H_{27}FN_3O_4$ $[M + H]^+$ 488.1980; found 488.1983. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol, 88:12, flow rate: 1.0 mL/min, wavelength: 220 nm): R_t = 8.14 min (major, major diastereomer).

(5*S*,6*R*,8*S*,9*S*,10*S*)-8-(4-Bromophenyl)-6-hydroxy-4,6-dimethyl-9-nitro-2,10-diphenyl-2,3-diazaspiro[4.5]dec-3-en-1-one (4da): Yellow solid, 52 % yield, m.p. 171–175 °C. $[\alpha]_D^{20}$ = +56.4 (*c* = 1.0, $CHCl_3$). >20:1 *dr*, >99 % *ee* for the major diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 8.4 Hz, 2 H), 7.47 (d, *J* = 8.4 Hz, 2 H), 7.40 (t, *J* = 8.0 Hz, 2 H), 7.30 (d, *J* = 8.8 Hz, 2 H), 7.14–7.25 (m, 6 H), 5.99 (t, *J* = 11.6 Hz, 1 H), 4.29 (d, *J* = 11.6 Hz, 1 H), 3.83 (ddd, *J* = 13.2, 11.6, 4.4 Hz, 1 H), 3.12 (dd, *J* = 14.4, 13.6 Hz, 1 H), 2.25 (s, 3 H), 1.76 (dd, *J* = 14.8, 4.4 Hz, 1 H), 1.71 (s, 1 H), 1.22 (s, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 172.5, 160.8, 138.2, 137.0, 133.2, 132.1, 129.3, 128.9 (2 C), 126.0, 121.9, 119.9, 90.0, 72.3, 65.9, 46.8, 43.3, 40.8, 26.0, 17.4 ppm. HRMS (ESI): *m/z* calcd. for $C_{28}H_{27}BrN_3O_4$ $[M + H]^+$ 548.1179; found 548.1175. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol, 88:12, flow rate: 1.0 mL/min, wavelength: 220 nm): R_t = 7.49 (minor, major diastereomer) and 9.26 min (major, major diastereomer).

(5*S*,6*R*,8*S*,9*S*,10*S*)-6-Hydroxy-4,6-dimethyl-9-nitro-8-(4-nitrophenyl)-2,10-diphenyl-2,3-diazaspiro[4.5]dec-3-en-1-one (4ea): Pale yellow solid, 51 % yield, m.p. 152–156 °C. $[\alpha]_D^{20}$ = +70.4 (*c* = 1.0, $CHCl_3$). >20:1 *dr*, >99 % *ee* for the major diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22 (d, *J* = 8.4 Hz, 2 H), 7.66 (d, *J* = 8.4 Hz, 2 H), 7.61 (d, *J* = 8.4 Hz, 2 H), 7.41 (t, *J* = 7.6 Hz, 2 H), 7.16–7.25 (m, 6 H), 6.05 (t, *J* = 11.6 Hz, 1 H), 4.32 (d, *J* = 12.0 Hz, 1 H), 4.01 (ddd, *J* = 12.8, 11.6, 4.4 Hz, 1 H), 3.18 (t, *J* = 14.0 Hz, 1 H), 2.26 (s, 3 H), 1.81 (dd, *J* = 14.4, 4.4 Hz, 1 H), 1.75 (s, 1 H), 1.26 (s, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 172.5, 160.6, 147.6, 146.8, 136.9, 132.9, 129.0, 128.9 (2 C), 128.7, 126.1, 124.2, 119.9, 89.7, 72.1, 65.9, 46.6, 43.6, 40.5, 25.9, 17.4 ppm. HRMS (ESI): *m/z* calcd. for $C_{28}H_{27}N_4O_6$ $[M + H]^+$ 515.1925; found 515.1925. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol, 88:12, flow rate: 1.0 mL/min, wavelength: 220 nm): R_t = 7.02 (minor, minor diastereomer), 7.47 (major, minor diastereomer) and 13.23 min (major, major diastereomer).

(5*S*,6*R*,8*S*,9*S*,10*S*)-8-(2-Furyl)-6-hydroxy-4,6-dimethyl-9-nitro-2,10-diphenyl-2,3-diazaspiro[4.5]dec-3-en-1-one (4fa): Yellow solid, 65 % yield, m.p. 88–90 °C. $[\alpha]_D^{20}$ = +78.2 (*c* = 1.0, $CHCl_3$). >20:1 *dr*, >99 % *ee* for the major diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 7.6 Hz, 2 H), 7.41 (br. s, 1 H), 7.39 (t, *J* = 8.0 Hz, 2 H), 7.13–7.25 (m, 7 H), 6.98 (t, *J* = 7.2 Hz, 1 H), 6.87 (d, *J* = 8.4 Hz, 1 H), 6.24 (br. s, 1 H), 4.43 (br. s, 1 H), 4.31 (d, *J* = 12.0 Hz, 1 H), 3.87 (s, 3 H), 3.12 (br. s, 1 H), 2.27 (s, 3 H), 1.85 (s, 1 H), 1.74 (dd, *J* = 14.4, 4.0 Hz, 1 H), 1.19 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.5, 161.0, 157.0, 137.1, 133.6, 129.3, 129.0, 128.8 (2 C), 128.7, 125.8, 121.1, 120.1, 119.8, 111.2, 110.9, 88.4, 72.5, 66.1, 55.7, 47.0, 44.4, 35.3, 26.0, 17.5 ppm. HRMS (ESI): *m/z* calcd. for $C_{29}H_{30}N_3O_5$ $[M + H]^+$ 500.2180; found 500.2187. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol, 88:12, flow rate: 1.0 mL/min, wavelength: 220 nm): R_t = 8.23 (major, major diastereomer), 11.40 (minor, minor diastereomer) and 14.80 min (major, minor diastereomer).

(5*S*,6*R*,8*R*,9*R*,10*S*)-8-(2-Furyl)-6-hydroxy-4,6-dimethyl-9-nitro-2,10-diphenyl-2,3-diazaspiro[4.5]dec-3-en-1-one (4ga): Yellow solid, 60 % yield, m.p. 189–192 °C. $[\alpha]_D^{20}$ = +96.3 (*c* = 1.0, $CHCl_3$). >20:1 *dr*, >99 % *ee* for the major diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 8.0 Hz, 2 H), 7.35–7.39 (m, 3 H), 7.17–7.26 (m, 6 H), 6.30 (s, 1 H), 6.23 (s, 1 H), 5.98 (t, *J* = 11.6 Hz, 1 H), 4.25 (d, *J* = 12.0 Hz, 1 H), 4.06 (dt, *J* = 11.6, 3.6 Hz, 1 H), 3.22 (t, *J* = 14.0 Hz, 1 H), 2.25 (s, 3 H), 1.87 (dd, *J* = 14.4, 3.6 Hz, 1 H), 1.70 (s, 1 H), 1.23 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.2, 160.6, 152.2, 142.5, 137.0, 133.1, 128.8 (2 C), 125.8, 119.7, 110.3, 107.0, 88.3, 72.2, 65.8, 46.7, 38.3, 37.2, 26.1, 17.5 ppm. HRMS (ESI): *m/z* calcd. for $C_{26}H_{26}N_3O_5$ $[M + H]^+$ 460.1867; found 460.1872. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol, 95:5, flow rate: 1.0 mL/min, wavelength: 220 nm): R_t = 12.65 (major, minor diastereomer) and 24.48 min (major, major diastereomer).

Supporting Information (see footnote on the first page of this article): Copies of NMR, HRMS, and chiral HPLC spectra of the prepared optically active 3,4-dihydrothiacarbazol-2(9*H*)-ones are provided.

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[15] CCDC 1434375 (for **4ac**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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