Organocatalytic One-Pot Asymmetric Synthesis of Functionalized Spiropyrazolones via a Michael-Aldol Sequential Reaction

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Experimental section

General remarks

All reagents were used as purchased from commercial suppliers without further purification. IR spectra were recorded on a Perkin-Elmer 500 spectrometer. NMR spectra were recorded on a Bruker Avance 400 NMR spectrometer (400 MHz for $^1$H and 100 MHz for $^{13}$C). Chemical shifts are reported in $\delta$ parts per million referenced to an internal TMS standard for $^1$H NMR and chloroform-d ($\delta$ 77.2 ppm) for $^{13}$C NMR. Optical rotations were measured on a JASCO P-2000 polarimeter HRMS spectra were recorded on Waters Xevo G2-S Tof. The X-ray diffraction measurements were carried out at 296 K on a KAPPA APEX II CCD area detector system equipped with a graphite monochromator and a Mo-Ka fine-focus sealed tube ($k = 0.71073$ Å). Routine monitoring of reactions was performed using silica gel, glass-backed TLC plates (Merck Kieselgel 60F$_{254}$) and visualized by UV light (254 nm). Solutions were evaporated to dryness under reduced pressure on a rotary evaporator and the residues purified by flash column chromatography on silica gel (230-400 mesh) with the indicated eluents.

General procedure: To a stirred solution of 3-methyl-1-phenyl-2-pyrazolin-5-one (1) (0.2 mmol) and catalyst (2 mol %) in CH$_2$Cl$_2$ (0.6 mL) solvent was added (E)-5-nitro-6-aryl-hex-5-en-2-one (2) (0.2 mmol). The reaction mixture was stirred at room temperature (25-30 °C) until the completion of 3-methyl-1-phenyl-2-pyrazolin-5-one and monitored by TLC. After completion of pyrazolinone, DIPEA were added subsequently and further stirred for indicated time at room temperature and CH$_2$Cl$_2$ was evaporated off. After removal of the solvent, a crude residue was purified by flash column chromatography (hexanes/ethyl acetate = 4:1~3:1) to afford the pure spirocyclohexane pyrazolone derivatives (3a-3p).

The diastereomeric ratios were determined from the crude reaction mixture measured in $^1$H NMR spectra. Some compounds were isolated as mixture of diastereomers after flash column chromatography. The $^1$H and $^{13}$C NMR data of the major isomers were given.
(5R,6S,9R,10R)-6-hydroxy-4,6-dimethyl-9-nitro-2,10-diphenyl-2,3-diazaspiro[4.5]dec-3-en-1-one (3a):
White solid, Yield: 61%, mp 140-142 °C; [α]25.6 D = -155.6 (c = 0.5 in CH₂Cl₂); IR (KBr): ν 3568, 2918, 2850, 2378, 1773, 1694, 911, 759, 691 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.58 (d, 2H, J = 7.8 Hz), 7.35(t, 2H, J = 7.8 Hz), 7.20-7.14 (m, 6H), 5.84 (td, 1H, J = 11.7, 4.3 Hz), 4.12 (d, 1H, J = 11.7 Hz), 2.85 (td, 1H, J = 14.1, 4.3 Hz), 2.59-2.48 (m, 1H), 2.38-2.35 (m, 1H), 2.24 (s, 3H), 1.73 (s, 1H), 1.65 (m, 1H), 1.16 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 172.6, 161.0, 137.2, 134.0, 129.0, 128.9, 128.8, 126.0, 120.0, 84.5, 72.1, 66.4, 46.1, 33.0, 27.1, 26.3, 17.7. HRMS (ESI) m/z: [M+H]⁺ calcd. for C₂₂H₂₄N₃O₄ 394.1767; found 394.1765. The ee value of 3a was 92% determined by HPLC with chiralpak AD-H column (i-PrOH/hexanes: 8/92; flow rate: 0.7 mL/min; λ 254 nm); t_R (major) 11.69 min; t_R (minor) 19.84 min.

(5R,6S,9R,10R)-6-hydroxy-10-(4-methoxyphenyl)-4,6-dimethyl-9-nitro-2-phenyl-2,3-diazaspiro[4.5]dec-3-en-1-one (3b):
White solid, Yield: 53%, mp 74-76 °C; [α]25.6 D = -106.9 (c = 0.5 in CH₂Cl₂); IR (KBr): ν 3543, 2916, 2849, 2352, 1715, 1695, 1371, 1032, 757 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.63-7.61 (m, 2H), 7.36 (t, 2H, J = 7.7 Hz), 7.19 (t, 1H, J = 7.7 Hz), 7.11 (d, 2H, J = 8.7 Hz), 6.67 (d, 2H, J = 8.7 Hz) 5.79 (td, 1H, J = 11.8, 4.4 Hz), 4.06 (d, 1H, J = 11.8 Hz), 3.67 (s, 3H), 2.83 (td, 1H, J =
14.2, 4.4 Hz), 2.58-2.48 (m, 1H), 2.38-2.32 (m, 1H), 2.23 (s, 3H), 1.69 (s, 1H), 1.66-1.62 (m, 1H), 1.16 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 172.7, 161.1, 159.7, 137.3, 129.0, 125.9 (2C), 119.9, 114.3, 84.8, 72.2, 66.5, 55.3, 45.4, 33.0, 27.1, 26.3, 17.6. HRMS (ESI) m/z: [M+H]$^+$ calcd. for C$_{23}$H$_{26}$N$_3$O$_5$ 424.1872; found 424.1874. The ee value of 3b was 92% determined by HPLC with chiralpak OJ-H column (i-PrOH/hexanes: 8/92; flow rate: 0.6 mL/min; $\lambda$ 254 nm); $t_R$ (minor) 60.26 min; $t_R$ (major) 78.89 min.


White solid, Yield: 55%, mp 88-90 °C; [\(\alpha\)]$_D$ -129.8 (c = 0.5 in CH$_2$Cl$_2$); IR (KBr): $\nu$ 3588, 2916, 2849, 1698, 1654, 1551, 1293 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.63-7.61 (m, 2H), 7.38-7.34 (m, 2H), 7.21-7.17 (m, 1H), 7.07 (d, 2H, $J$ = 8.2 Hz), 6.96-6.93 (m, 2H), 5.82 (td, 1H, $J$ = 11.8, 4.4 Hz), 4.07 (d, 1H, $J$ = 11.8 Hz), 2.85 (td, 1H, $J$ = 14.2, 4.4 Hz), 2.58-2.48 (m, 1H), 2.39-2.33 (m, 1H), 2.24 (s, 3H), 2.19 (s, 3H), 1.66-1.64 (m, 2H), 1.16 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 172.7, 161.1, 138.5, 137.3, 130.9, 129.6, 129.0, 125.9, 120.0, 84.7, 72.2, 66.4, 45.8, 33.0, 27.1, 26.3, 21.1, 17.7. HRMS (ESI) m/z: [M+H]$^+$ calcd. for C$_{23}$H$_{26}$N$_3$O$_4$ 408.1923; found 408.1923. The ee value of 3c was 86% determined by HPLC with chiralpak AD-H column (i-PrOH/hexanes: 6/94; flow rate: 0.7 mL/min; $\lambda$ 254 nm); $t_R$ (minor) 56.34 min; $t_R$ (major) 75.17 min.
(5R,6S,9R,10R)-6-hydroxy-10-(4-isobutylphenyl)-4,6-dimethyl-9-nitro-2-phenyl-2,3-diazaspiro[4.5]dec-3-en-1-one (3d):

White solid, Yield: 50%, mp 76-78 °C; [α]D = -134.0 (c = 0.5 in CH2Cl2); IR (KBr): ν 3585, 2955, 2924, 2356, 1715, 1551, 1368, 1249, 865, 757, 690 cm⁻¹; ¹H NMR (400 MHz, CDCl3): δ 7.55-7.53 (m, 2H), 7.36-7.31 (m, 2H), 7.20-7.15 (m, 1H), 7.09-7.07 (m, 1H), 6.91-6.88 (m, 2H), 5.82 (td, 1H, J = 11.8, 4.4 Hz), 4.08 (d, 1H, J = 11.8 Hz), 2.85 (td, 1H, J = 14.2, 4.4 Hz), 2.59-2.48 (m, 1H), 2.39-2.34 (m, 1H), 2.32-2.29 (m, 2H), 2.24 (s, 3H), 1.74-1.67 (m, 2H), 1.66-1.61 (m, 2H), 1.16 (s, 3H), 0.77 (q, 6H, J = 6.6 Hz); ¹³C NMR (100 MHz, CDCl3): δ 172.7, 161.0, 142.2, 137.3, 131.1, 129.5, 128.9, 125.9, 120.1, 84.5, 72.1, 66.5, 45.8, 45.0, 33.0, 30.1, 27.1, 26.3, 22.5, 22.4, 17.7. HRMS (ESI) m/z: [M+H]+ calcd. for C₂₆H₃₂N₃O₄ 450.2393; found 450.2394. The ee value of 3d was 86% determined by HPLC with chiralpak AS-H column (i-PrOH/hexanes: 8/92; flow rate: 0.7 mL/min; λ 254 nm); tᵣ (major) 13.48 min; tᵣ (minor) 45.06 min.
White solid, Yield: 58%, mp 138-140 °C; [α]25.6 D = -219.0 (c = 0.5 in CH₂Cl₂); IR (KBr): ν 3655, 3593, 2917, 2850, 2358, 1715, 1651, 1495 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.62 (d, 2H, J = 7.7 Hz), 7.35 (t, 2H, J = 7.9 Hz), 7.18 (t, 1H, J = 7.8 Hz), 7.06 (t, 1H, J = 7.8 Hz), 6.78 (d, 1H, J = 7.8 Hz), 6.78 (d, 1H, J = 7.8 Hz), 6.71-6.68 (m, 2H), 5.83 (td, 1H, J = 11.8, 4.5 Hz), 4.09 (d, 1H, J = 11.8 Hz), 3.54 (s, 3H), 2.87 (td, 1H, J = 14.1, 4.4 Hz), 2.59-2.49 (m, 1H), 2.41-2.35 (m, 1H), 2.25 (s, 3H), 1.68-1.62 (m, 1H), 1.59 (s, 1H), 1.19 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 172.7, 161.0, 159.8, 137.3, 135.5, 129.9, 129.0, 125.9, 119.8, 114.7, 84.5, 72.2, 66.3, 55.1, 46.2, 33.0, 27.1, 26.3, 17.7. HRMS (ESI) m/z: [M+H]+ calcd. for C₂₃H₂₆N₃O₄ 424.1872; found 424.1874. The ee value of 3e was 92% determined by HPLC with chiralpak AD-H column (i-PrOH/hexanes: 8/92; flow rate: 0.7 mL/min; λ 254 nm); tᵣ (major) 15.49 min; tᵣ (minor) 24.61 min.

White solid, Yield: 37%, mp 108-110 °C; [α]25.6 D = -109.7 (c = 0.5 in CH2Cl2); IR (KBr): ν 3543, 2919, 2850, 2357, 1715, 1557, 1496, 758 cm⁻¹; ¹H NMR (400 MHz, CDCl3): δ 7.64-7.61 (m, 2H), 7.41-7.34 (m, 3H), 7.34-7.31 (m, 1H), 7.25-7.21 (m, 1H), 7.18-7.16 (m, 1H), 7.04 (t, 1H, J = 7.8 Hz), 5.82 (td, 1H, J = 11.8, 4.5 Hz), 4.12 (d, 1H, J = 11.8 Hz), 2.88 (td, 1H, J = 14.1, 4.4 Hz), 2.61-2.50 (m, 1H), 2.44-2.38 (m, 1H), 2.27 (s, 3H), 1.70-1.65 (m, 2H), 1.21 (s, 3H); ¹³C NMR (100 MHz, CDCl3): δ 172.3, 160.6, 136.5, 132.0, 130.5, 129.0, 126.2, 120.2, 84.2, 72.2, 66.2, 45.7, 33.0, 27.1, 26.3, 17.7. HRMS (ESI) m/z: [M+H]$^+$ calcd. for C22H23N3O4Br 472.0872; found 472.0874. The ee value of 3f was 88% determined by HPLC with chiralpak AD-H column (i-PrOH/hexanes: 8/92; flow rate: 0.7 mL/min; λ 254 nm); tᵣ (major) 12.38 min; tᵣ (minor) 16.78 min.
\((5R,6S,9R,10R)-10-(4\text{-bromophenyl})-6\text{-hydroxy}-4,6\text{-dimethyl}-9\text{-nitro}-2\text{-phenyl}-2,3\text{-diazaspiro}[4.5]\text{dec}-3\text{-en}-1\text{-one}\) (3g):

White solid, Yield: 42%, mp 105-107 °C. \([\alpha]_{25.6}^\circ D = -130.0\) (c = 0.5 in CH\(_2\)Cl\(_2\)); IR (KBr): \(\nu\) 3566, 2920, 2341, 2359, 1715, 1496, 1076, 756, 690 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.63-7.60 (m, 2H), 7.44-7.35 (m, 3H), 7.30-7.28 (m, 2H), 7.23-7.19 (m, 1H), 7.08 (d, 2H, \(J = 8.5\) Hz), 5.79 (td, 1H, \(J = 11.8, 4.4\) Hz), 4.10 (d, 1H, \(J = 11.8\) Hz), 2.85 (td, 1H, \(J = 14.2, 4.4\) Hz), 2.59-2.48 (m, 1H), 2.41-2.35 (m, 1H), 2.23 (s, 3H), 1.68-1.63 (m, 1H), 1.59 (s, 1H), 1.18 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 172.4, 160.7, 137.2, 133.2, 132.2, 129.1, 126.1, 123.0, 119.8, 84.3, 72.2, 66.2, 45.5, 33.0, 27.0, 26.3, 17.7. HRMS (ESI) m/z: [M+H]\(^+\) calcd. for C\(_{22}\)H\(_{23}\)N\(_3\)O\(_4\)Br 472.0872; found 472.0874. The ee value of 3g was 94% determined by HPLC with chiralpak OJ-H column (i-PrOH/hexanes: 8/92; flow rate: 0.6 mL/min; \(\lambda\) 254 nm); \(t_R\) (minor) 33.63 min; \(t_R\) (major) 40.74 min.
(5R,6S,9R,10R)-10-(4-chlorophenyl)-6-hydroxy-4,6-dimethyl-9-nitro-2-phenyl-2,3-diazaspiro[4.5]dec-3-en-1-one (3h):

White solid, Yield: 54%, mp 100-102 °C; [α]25.6 D = -101.5 (c = 0.5 in CH2Cl2); IR (KBr): ν 3566, 2916, 2850, 2357, 1715, 1595, 1093, 690 cm⁻¹; ¹H NMR (400 MHz, CDCl3): δ 7.65-7.62 (m, 2H), 7.42-7.37 (m, 2H), 7.25-7.19 (m, 1H), 7.16-7.14 (m, 4H), 5.82 (td, 1H, J = 11.8, 4.4 Hz), 4.14 (d, 1H, J = 11.8 Hz), 2.86 (td, 1H, J = 14.2, 4.4 Hz), 2.61-2.50 (m, 1H), 2.43-2.37 (m, 1H), 2.26 (s, 3H), 1.75 (s, 1H), 1.70-1.65 (m, 1H), 1.19 (s, 3H); ¹³C NMR (100 MHz, CDCl3): δ 172.4, 160.7, 137.1, 134.8, 132.7, 129.2, 129.1, 126.1, 119.8, 84.4, 72.2, 66.3, 45.5, 32.9, 27.0, 26.2, 17.7. HRMS (ESI) m/z: [M+H]+ calcd. for C₂₂H₂₃N₃O₄Cl 428.1377; found 428.1381. The ee value of 3h was 92% determined by HPLC with chiralpak AS-H column (i-PrOH/hexanes: 6/94; flow rate: 0.6 mL/min; λ 254 nm); tᵣ (major) 32.41 min; tᵣ (minor) 54.37 min.
(5R,6S,9R,10R)-10-(4-fluorophenyl)-6-hydroxy-4,6-dimethyl-9-nitro-2-phenyl-2,3-
diazaspiro[4.5]dec-3-en-1-one (3i):

White solid, Yield: 80%, mp 81-83 °C; [α]$_{25.6}$ D = -118.3 (c = 0.5 in CH$_2$Cl$_2$); IR (KBr): ν 3546, 2916, 2850, 2358, 1715, 1695, 1371, 1163, 1034, 915, 691 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 7.61-7.59 (m, 2H), 7.38-7.34 (m, 2H), 7.22-7.17 (m, 3H), 6.87-6.83 (m, 2H), 5.80 (td, 1H, J = 11.8, 4.4 Hz), 4.12 (d, 1H, J = 11.8 Hz), 2.84 (td, 1H, J = 14.1, 4.4 Hz), 2.59-2.48 (m, 1H), 2.40-2.35 (m, 1H), 2.24 (s, 3H), 1.69 (s, 1H), 1.67-1.62 (m, 1H), 1.17 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 172.5, 162.7 (d, $^1$J$_{CF} = 248.0$ Hz) 160.9, 137.1, 129.9 (d, $^4$J$_{CF} = 3.26$ Hz), 129.1, 126.1, 119.9, 116.0 (d, $^2$J$_{CF} = 22.0$ Hz), 115.9, 84.5, 72.1, 66.4, 45.3, 32.9, 27.0, 26.3, 17.7. HRMS (ESI) m/z: [M+H]$^+$ calcd. for C$_{22}$H$_{23}$N$_3$O$_4$F 412.1673; found 412.1672. The ee value of 3i was 90% determined by HPLC with chiralpak AS-H column (i-PrOH/hexanes: 8/92; flow rate: 0.7 mL/min; λ 254 nm); t$_R$ (major) 24.78 min; t$_R$ (minor) 41.21 min.

White solid, Yield: 54%, mp 95-97 °C; [α]25.6 D= -131.2 (c = 0.5 in CH₂Cl₂); IR (KBr): ν 3587, 2916, 2850, 2356, 1715, 1694, 1371, 1034, 738, 696 cm⁻¹; ^1H NMR (400 MHz, CDCl₃): δ 7.60-7.58 (m, 2H), 7.39-7.35 (m, 2H), 7.22-7.18 (m, 2H), 7.17-7.14 (m, 1H), 7.10-7.08 (m, 2H), 5.81 (td, 1H, J = 11.8, 4.5 Hz), 4.11 (d, 1H, J = 11.8 Hz), 2.85 (td, 1H, J = 14.2, 4.4 Hz), 2.58-2.48 (m, 1H), 2.42-2.37 (m, 1H), 2.25 (s, 3H), 1.68-1.63 (m, 2H), 1.18 (s, 3H); ^13C NMR (100 MHz, CDCl₃): δ 172.3, 160.7, 137.1, 136.2, 134.8, 130.2, 129.1, 129.0, 126.2, 120.1, 84.2, 72.2, 66.1, 45.7, 33.0, 27.1, 26.3, 17.7. HRMS (ESI) m/z: [M+H]^+ calcd. for C₂₂H₂₃N₃O₄Cl 428.1377; found 428.1377. The ee value of 3j was 90% determined by HPLC with chiralpak AD-H column (i-PrOH/hexanes: 8/92; flow rate: 0.7 mL/min; λ 254 nm); tᵣ (major) 12.18 min; tᵣ (minor) 16.53 min.
(5R,6S,9R,10R)-6-hydroxy-4,6-dimethyl-9-nitro-10-(4-nitrophenyl)-2-phenyl-2,3-diazaspiro[4.5]dec-3-en-1-one (3k):

White solid, Yield: 53%, mp 159-161 °C; [α]25.6 D = -117.0 (c = 0.5 in CH₂Cl₂); IR (KBr): ν 3566, 2916, 2849, 1715, 1695, 1348, 740 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 8.03 (d, 2H, J = 8.8 Hz), 7.61-7.59 (m, 2H), 7.42-7.35 (m, 4H), 7.23-7.20 (m, 1H), 5.86 (td, 1H, J = 11.7, 4.5 Hz), 4.29 (d, 1H, J = 11.7 Hz), 2.86 (td, 1H, J = 14.1, 4.5 Hz), 2.62-2.51 (m, 1H), 2.45-2.40 (m, 1H), 2.25 (s, 3H), 1.80 (s, 1H), 1.73-1.67 (m, 1H), 1.20 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 172.0, 160.4, 148.1, 141.8, 136.9, 129.2, 126.3, 124.1, 119.6, 84.0, 72.1, 66.1, 45.7, 32.9, 27.0, 26.2, 17.7.. HRMS (ESI) m/z: [M+H]⁺ calcd. for C₂₂H₂₃N₄O₆ 439.1618; found 439.1621. The ee value of 3k was 90% determined by HPLC with chiralpak AD-H column (i-PrOH/hexanes: 10/90; flow rate: 1 mL/min; λ 254 nm); tᵣ (minor) 10.04 min; tᵣ (major) 13.44 min.
(5R,6S,9R,10R)-6-hydroxy-4,6-dimethyl-9-nitro-2-phenyl-10-(thiophen-2-yl)-2,3-diazaspiro[4.5]dec-3-en-1-one (3l):

White solid, Yield: 53%, mp 72-74 °C; [α]D25.6 D= -100.3 (c = 0.5 in CH2Cl2); IR (KBr): v 3567, 2916, 2850, 2427, 1696, 1552, 1295, 739 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.69-7.67 (m, 2H), 7.39-7.35 (m, 2H), 7.21-7.19 (m, 1H), 7.08-7.07 (m, 1H), 6.90-6.89 (m, 1H), 6.79-6.77 (m, 1H), 5.77 (td, 1H, J = 11.7, 4.5 Hz), 4.43 (d, 1H, J = 11.7 Hz), 2.78 (td, 1H, J = 14.1, 4.4 Hz), 2.57-2.46 (m, 1H), 2.37-2.31 (m, 1H), 2.27 (s, 3H), 1.81 (s, 1H ), 1.65-1.60 (m, 1H), 1.18 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 172.3, 160.9, 137.4, 136.1, 129.0, 127.1, 125.9, 125.7, 119.8, 85.8, 72.2, 66.7, 41.2, 32.7, 27.0, 26.3, 17.6. HRMS (ESI) m/z: [M+H]⁺ calcd. for C₂₀H₂₂N₃O₄S 400.1331; found 400.1333. The ee value of 3l was 70% determined by HPLC with chiralpak AD-H column (i-PrOH/hexanes: 8/92; flow rate: 0.7 mL/min; λ 254 nm); tᵣ (major) 13.74 min; tᵣ (minor) 22.53 min.
(5R,6S,9R,10R)-6-hydroxy-4,6-dimethyl-10-(naphthalen-2-yl)-9-nitro-2-phenyl-2,3-diazaspiro[4.5]dec-3-en-1-one (3m):

White solid, Yield: 56%, mp 100-102 °C; [α]25.6 D = -122.8 (c = 0.5 in CH₂Cl₂); IR (KBr); ν 3565, 2919, 2356, 2329, 1715, 1695, 1496, 750 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.70-7.62 (m, 4H), 7.55 (d, 2H, J = 7.8 Hz), 7.40-7.38 (m, 2H), 7.33-7.29 (m, 3H), 7.19-7.15 (m, 1H), 5.95 (td, 1H, J = 11.8, 4.4 Hz), 4.30 (d, 1H, J = 11.8 Hz), 2.90 (td, 1H, J = 14.2, 4.4 Hz), 2.65-2.54 (m, 1H), 2.43-2.37 (m, 1H), 2.25 (s, 3H), 1.68 (s, 1H), 1.66-1.64 (m, 1H), 1.19 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 172.8, 161.0, 137.2, 133.4, 133.3, 131.6, 129.0, 128.1, 127.7, 126.5, 126.5, 126.0, 120.0, 84.7, 72.3, 66.4, 46.4, 33.0, 27.2, 26.3, 17.7. HRMS (ESI) m/z: [M+H]⁺ calcd. for C₂₆H₂₆N₃O₄ 444.1923; found 444.1924. The ee value of 3m was 90% determined by HPLC with chiralpak AD-H column (i-PrOH/hexanes: 5/95; flow rate: 0.5 mL/min; λ 254 nm); tᵣ (major) 47.39 min; tᵣ (minor) 58.29 min.
(5R,6S,9R,10R)-10-(benzo[d][1,3]dioxol-5-yl)-6-hydroxy-4,6-dimethyl-9-nitro-2-phenyl-2,3-
diazaspiro[4.5]dec-3-en-1-one (3n):

White solid, Yield: 51%, mp 99-101 °C; [α]$^25.6$ D = -107.4 (c = 0.5 in CH$_2$Cl$_2$); IR (KBr): ν 3586, 2916, 2849, 1695, 1715, 1495, 1244, 1038, 928, 756 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 7.63 (d, 2H, $J = 7.6$ Hz), 7.36 (t, 2H, $J = 7.9$ Hz), 7.19 (t, 1H, $J = 7.4$ Hz), 6.70-6.66 (m, 2H), 6.56 (d, 1H, $J = 8.0$ Hz), 5.84-5.84 (d, 1H, $J = 1.2$ Hz), 5.81 (s, 1H), 5.71 (td, 1H, $J = 11.8$, 4.4 Hz), 4.03 (d, 1H, $J = 11.8$ Hz), 2.81 (td, 1H, $J = 14.2$, 4.4 Hz), 2.56-2.46 (m, 1H), 2.37-2.31 (m, 1H), 2.24 (s, 3H), 1.68 (s, 1H), 1.64-1.60 (m, 1H), 1.15 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 172.6, 161.1, 147.8, 137.3, 129.0, 127.6, 126.0, 120.0, 108.6, 101.3, 84.8, 72.2, 66.5, 45.8, 32.9, 27.1, 26.3, 17.7. HRMS (ESI) m/z: [M+H]$^+$ calcd. for C$_{23}$H$_{26}$N$_3$O$_6$ 438.1665; found 438.1664. The ee value of 3n was 94% determined by HPLC with chiralpak OJ-H column (i-PrOH/hexanes: 8/92; flow rate: 1 mL/min; λ 254 nm); $t_R$ (minor) 44.01 min; $t_R$ (major) 54.89 min.
(5R,6S,9R,10R)-10-(6-chloropyridin-3-yl)-6-hydroxy-4,6-dimethyl-9-nitro-2-phenyl-2,3-
diazaspiro[4.5]dec-3-en-1-one (3o):

White solid, Yield: 40%, mp 98-100 °C; \([\alpha]_{25.6}^{25.6} = -219.0\) (c = 0.5 in CH$_2$Cl$_2$); IR (KBr): ν 3547, 3058, 2916, 2850, 2363, 2344, 1715, 1456, 1024, 838, 739, 692 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 8.24 (d, 1H, $J$ = 2.5 Hz), 7.64-7.62 (m, 2H), 7.53-7.50 (m, 1H), 7.40-7.36 (m, 2H), 7.24-7.20 (m, 1H), 7.10 (d, 1H, $J$ = 8.3 Hz), 5.78 (td, 1H, $J$ = 11.8, 4.5 Hz), 4.18 (d, 1H, $J$ = 11.8 Hz), 2.84 (td, 1H, $J$ = 14.2, 4.4 Hz), 2.61-2.54 (m, 1H), 2.43-2.39 (m, 1H), 2.26 (s, 3H), 1.72-1.66 (m, 2H), 1.20 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 172.0, 160.4, 152.1, 150.3, 137.0, 129.2, 126.3, 124.6, 119.6, 83.8, 72.1, 66.6, 45.7, 33.0, 30.0, 27.0, 26.3, 17.7. HRMS (ESI) m/z: [M+H]$^+$ calcd. for C$_{21}$H$_{22}$N$_4$O$_4$Cl 429.1330; found 429.1333. The ee value of 3o was 94% determined by HPLC with chiralpak OD-H column (i-PrOH/hexanes: 8/92; flow rate: 1 mL/min; λ 254 nm); $t_R$ (minor) 12.08 min; $t_R$ (major) 13.93 min.
(5R,6S,9R,10R)-2-(4-bromophenyl)-6-hydroxy-4,6-dimethyl-9-nitro-10-phenyl-2,3-
diazaspiro[4.5]dec-3-en-1-one (3p):

White solid, Yield: 67%, mp 79-81 °C; [α]25.6 D = -156.0 (c = 0.5 in CH₂Cl₂); IR (KBr): ν 3590, 2917, 2850, 1698, 1490, 1364, 703 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.55-7.53 (m, 2H), 7.47-7.44 (m, 2H), 7.15-7.15 (m, 5H), 5.81 (td, 1H, J = 11.8, 4.4 Hz), 4.11 (d, 1H, J = 11.8 Hz), 2.82 (td, 1H, J = 14.2, 4.4 Hz), 2.59-2.48 (m, 1H), 2.40-2.35 (m, 1H), 2.24 (s, 3H), 1.75 (s, 1H), 1.66-1.63 (m, 1H), 1.15 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 172.6, 161.3, 136.3, 133.9, 132.0, 128.9, 128.8, 121.1, 118.8, 84.4, 72.1, 66.5, 46.1, 33.0, 27.1, 26.3, 17.7. HRMS (ESI) m/z: [M+H]+ calcd. for C₂₂H₂₃N₃O₄Br 472.0872; found 472.0875. The ee value of 3p was 90% determined by HPLC with chiralpak AD-H column (i-PrOH/hexanes: 8/92; flow rate: 0.7 mL/min; λ 254 nm); tᵣ (major) 14.36 min; tᵣ (minor) 23.14 min.
$^1$H and $^{13}$C NMR spectral copies:
(5R,6S,9R,10R)-6-hydroxy-4,6-dimethyl-9-nitro-2,10-diphenyl-2,3-diazaspiro[4.5]dec-3-en-1-one (3a):
(5R,6S,9R,10R)-6-hydroxy-10-(4-methoxyphenyl)-4,6-dimethyl-9-nitro-2-phenyl-2,3-diazaspiro[4.5]dec-3-en-1-one (3b):
(5R,6S,9R,10R)-6-hydroxy-10-(4-isobutylphenyl)-4,6-dimethyl-9-nitro-2-phenyl-2,3-diazaspiro[4.5]dec-3-en-1-one (3d):

Current Data Parameters
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PROCNO: 3

P2 - Acquisition Parameters
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INSTRUM: spect
PROBN: 5
PLH2PROG: 20
CPU: 32768

PROCNO: 3

P2 - Processing parameters
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SR: 409.1372513 MHz
DW: 0.50 sec
LB: 0.00 sec
PC: 1.00

Current Data Parameters
NAME: MBAM3-3
PROCNO: 3

P2 - Acquisition Parameters
DEFL: 261503
INSTRUM: spect
PROBN: 5
PLH2PROG: 20
CPU: 32768

PROCNO: 3

P2 - Processing parameters
IR: 4344
SR: 409.1372513 MHz
DW: 0.50 sec
LB: 0.00 sec
PC: 1.00
23

\[
\text{23, S, 9, 10, R, 6-hydroxy-10-(3-methoxyphenyl)-4,6-dimethyl-9-nitro-2-phenyl-2,3-diazaspiro[4.5]dec-3-en-1-one (3e):}
\]
(5R,6S,9R,10R)-10-(4-bromophenyl)-6-hydroxy-4,6-dimethyl-9-nitro-2-phenyl-2,3-diazaspiro[4.5]dec-3-en-1-one (3g):
(5R,6S,9R,10R)-10-(4-chlorophenyl)-6-hydroxy-4,6-dimethyl-9-nitro-2-phenyl-2,3-diazaspiro[4.5]dec-3-en-1-one (3h):
(5R,6S,9R,10R)-10-(4-fluorophenyl)-6-hydroxy-4,6-dimethyl-9-nitro-2-phenyl-2,3-diazaspiro[4.5]dec-3-en-1-one (3i):

Current Data Parameters
NAME: NDVYK_Pyrrolidine_TG
PROCNO: 1
PROCNO RT

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T1 15.00000000 Hz
T2 15.00000000 Hz

--- CHANNEL E2 ---
SPC 400.132800 MHz
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T1 15.00000000 Hz
T2 15.00000000 Hz

--- CHANNEL E3 ---
SPC 400.132800 MHz
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T1 15.00000000 Hz
T2 15.00000000 Hz

--- CHANNEL E4 ---
SPC 400.132800 MHz
H 15 13.9853 sec
T1 15.00000000 Hz
T2 15.00000000 Hz
(5R,6S,9R,10R)-6-hydroxy-4,6-dimethyl-9-nitro-10-(4-nitrophenyl)-2-phenyl-2,3-diazaspiro[4.5]dec-3-en-1-one (3k):
(5R,6S,9R,10R)-6-hydroxy-4,6-dimethyl-9-nitro-2-phenyl-10-(thiophen-2-yl)-2,3-
diazaspiro[4.5]dec-3-en-1-one (3l):
(5R,6S,9R,10R)-6-hydroxy-4,6-dimethyl-10-(naphthalen-2-yl)-9-nitro-2-phenyl-2,3-diazaspiro[4.5]dec-3-en-1-one (3m):
(5R,6S,9R,10R)-10-(benzo[d][1,3]dioxol-5-yl)-6-hydroxy-4,6-dimethyl-9-nitro-2-phenyl-2,3-diazaspiro[4.5]dec-3-en-1-one (3n):
(5R,6S,9R,10R)-10-(6-chloropyridin-3-yl)-6-hydroxy-4,6-dimethyl-9-nitro-2-phenyl-2,3-diazaspiro[4.5]dec-3-en-1-one (3o):
(5R,6S,9R,10R)-2-(4-bromophenyl)-6-hydroxy-4,6-dimethyl-9-nitro-10-phenyl-2,3-diazaspiro[4.5]dec-3-en-1-one (3p):
X-ray crystallographic structure and crystal data for compound (3a): [CCDC: 1492783]

Table 1. Crystal data and structure refinement for a18203.

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<th>Property</th>
<th>Value</th>
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<td></td>
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<td></td>
<td>c = 21.3811(8) Å, γ = 90°</td>
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<td>Density (calculated)</td>
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<td>Description</td>
<td>Value</td>
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<td>Crystal size</td>
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