Supporting Information-I

Trienamine catalysed unprecedented remote olefin E/Z isomerisation/[4+2]-cycloaddition reaction to access spirooxindole hexahydroindoles

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1. EXPERIMENTAL SECTION

1.1 General Experimental Procedures

Nuclear Magnetic Resonance Spectroscopy: ^{1}H NMR spectra were acquired on Bruker AVIII400 (400 MHz) spectrometer and were referenced to TMS and residual non-deuterated solvent peak in CDCl3 (δ = 7.26). Chemical shifts (δH and δC) are reported in parts per million (ppm), with signal splitting recorded as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), and multiplet and unresolved peaks (m). Coupling constants (*J*) are mentioned in Hz and are presented as observed. ^{13}C NMR spectra were obtained on Bruker AVIII400 (100 MHz) spectrometers and were referenced to solvent peaks in CDCl3 (δ = 77.0). Where diastereomeric mixtures are formed, data is given for the major diastereomer.

Mass Spectrometry: High-resolution mass spectra (HRMS) were recorded by the Thermo Fisher spectrometer using electrospray ionisation (ESI^{+}). The parent ion$[M+H]^{+}$ $[M+Na]^{+}$ is calculated to 4 decimal places from the molecular formula, and all values are within a tolerance of 5 ppm.

Specific rotations: Optical rotations were recorded on an Anton Parr MCP100 polarimeter with a path length of 1 dm (using the sodium D line, 589 nm). Specific rotations ($[\alpha]^{D}$) are reported in units of 10^{-1} deg cm^2 g^{-1}. Concentrations are reported in g/mL. Temperatures are reported at °C (typically 25 °C).

Infrared Spectroscopy: Absorption spectra were obtained on a Shimadzu FT-IR spectrometer. Wavelengths of maximum absorbance (vmax) are quoted in wavenumbers (cm ^{1}). Only selected characteristic IR absorption data are provided for each compound.
High-Performance Liquid Chromatography: Chromatograms were obtained using Shimadzu UFLC SPD-M20A with a prominence diode array detector on a selected 254nm channel.

Single Crystal XRD: Data was collected from the Sophisticated Analytical Instrumental Facility, Indian Institute of Technology Madras- Chennai.

Materials*:*

Unless otherwise stated, all reactions were carried out in oven-dried glassware using anhydrous reaction solvents. All other commercially available reagents and solvents were used as received, dried, and purified before using standard procedures.

General Procedure A: *Preparation of pyrrolidine-tethered dienal*

1a-c were prepared by following the reported literature procedure.[1]

General Procedure B: *Preparation of oxindole olefins*

2a-2b' were synthesised using a literature report.[2]

General Procedure C: *Aminocatalytic [4+2]-annulation:*

To an oven-dried vial containing catalyst **3** (0.2 equiv.), benzoic acid (0.2 equiv.) and the oxindole olefin (1.0 equiv.) in toluene (0.1M) were stirred for 10 minutes. Then the pyrrolidine-tethered dienal (1.2 equiv.) was added and the resulting mixture was stirred at RT for 15 minutes to 5 hours, the crude product was directly purified by column chromatography.

General Procedure D: *Aminocatalytic [4+2]-annulation:*

To an oven-dried vial containing catalyst **3** (0.2 equiv.), benzoic acid (0.2 equiv.) and the pyrrolidine-tethered dienal (1.2 equiv.) in toluene (0.1M) were stirred for 10 minutes. Then oxindole olefin (1.0 equiv.) was added and the resulting mixture was stirred at RT for 12 hours, the crude product was directly purified by column chromatography.

General Procedure E: *Ramachary Reductive Coupling (RRC) Reaction:*

Into a glass vial L-proline (0.2 equiv.) was treated with product (+)-**4t** (1.0 equiv.)**,** malononitrile (1.0 equiv.) and Hantzsch ester (1.0 equiv.) in DCM as a solvent. After the completion of the reaction crude mixture was purified using column chromatography, and the resulting product (+)-**5t** was obtained as a white solid**.**[3]

General Procedure F: *Acetal Protection Reaction:*

Into a glass vial, *p*-TSA (0.2 equiv.) and trimethyl orthoformate (3 equiv.) were treated with the product (+)-**4s** (1.0 equiv.) in MeOH as a solvent at 60° C for 15 minutes. After the completion of the reaction crude mixture was purified using column chromatography, and the resulting product (+)-**6s** was obtained as a white solid**.**[4]

General Procedure G: *$NaBH_4$ reduction:*

Into a 5 ml RBF (+)-**6s** was taken in MeOH, and $NaBH_4$ were added at -20° C and stirred overnight by slowly brought to RT and heated for 15 min. at 50° C. After the completion of the reaction, the crude product was quenched using sat. $NaHCO_3$ solution and extracted with EtOAc. Then the concentrated material was purified by column chromatography, and the product (+)-**7s** was obtained as a white solid.[4]

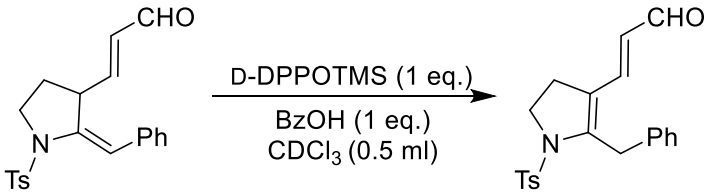
General Procedure H: *Fluoroetherification:*

Into a glass vial (+)-**7s** was taken in acetone (0.1 M), then select fluor (2 equiv.), and $NaHCO_3$ (2 equiv.) were added and stirred overnight at room temperature. The crude mixture was subjected to column chromatography to yield pure (+)-**8s** as a white solid.[5]

References

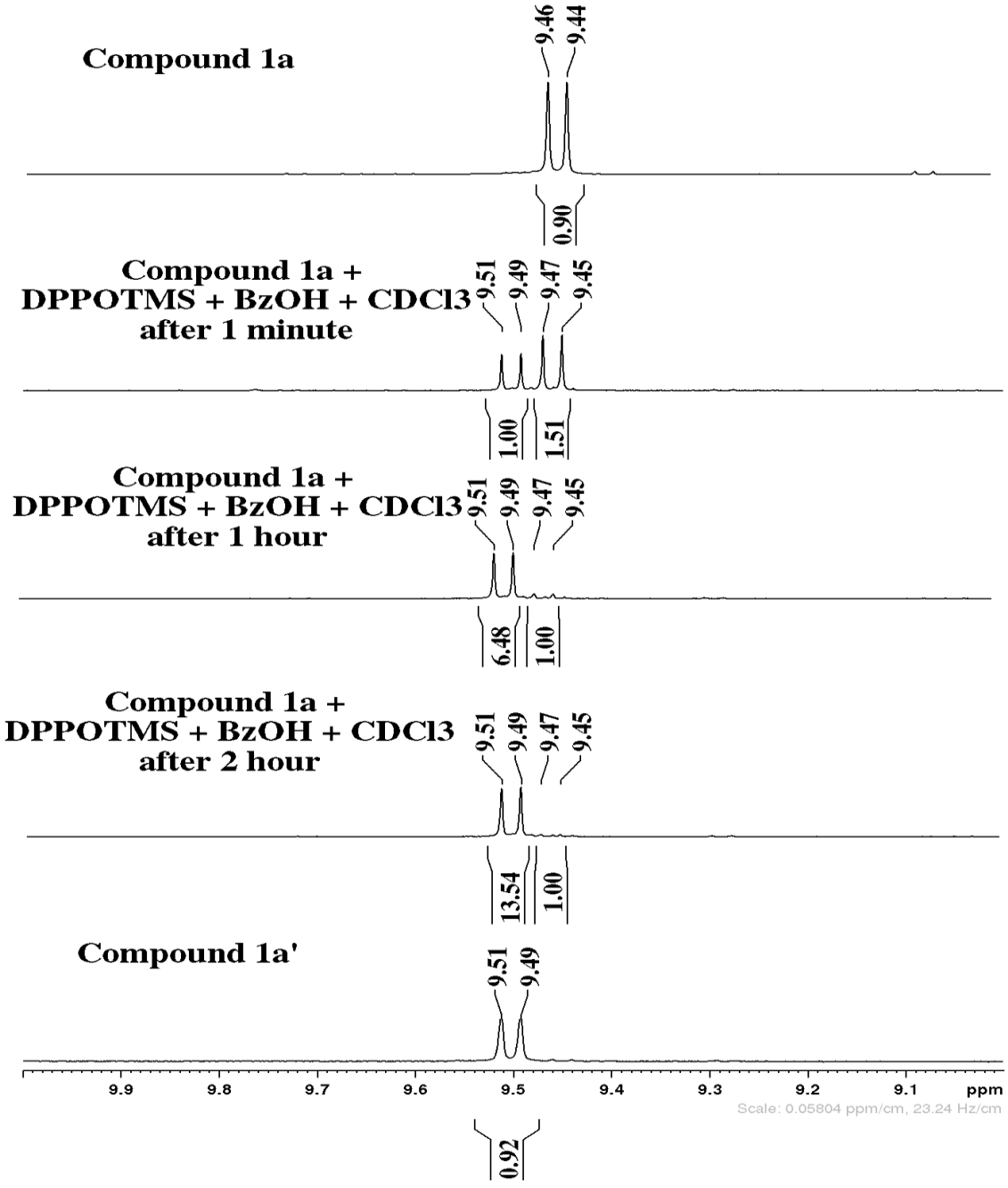
1) a) D. C. Braddock, R. Bhuva, D. S. Millan, Y. Perez-Fuertes, C. A. Roberts, R. N. Shepperd, S. Solanki, E. S. E. Stokes, A. J. P. White, *Org. Lett.* 2007, **9**, 3, 445-448. b) V. Chintalapudi, E. A. Galvin, R. L. Greenaway, E. A. Anderson, *Chem. Commun.,* 2016, **52**, 693. c) A. Mekareeya, P. R. Walker, A. Couce-Rios, C. D. Campbell, A. Steven, R. S. Paton, E. A. Anderson, *J. Am. Chem. Soc.,* 2017, **139**, 10104−10114.
2) a) H-B. Yang, Y-Z. Zhao, R. Sang, Y. Wei, and M. Shi, *Adv. Synth. Catal.* 2014, **356**, 3799-3808. b) S-H Cao, X-C Zhang, Y. Wei and M. Shi, *Eur. J. Org. Chem.* 2011, 2668–2672.
3) a) D. B. Ramachary and M. Kishor, *J. Org. Chem*., 2007, **72**, 5056; (b) D. B. Ramachary and Y. V. Reddy, *J. Org. Chem*., 2010, **75**, 74; (c) D. B. Ramachary and M. Kishor, Org. Biomol. Chem., 2010, **8**, 2859 and references cited therein. d) D. B. Ramachary, M. A. Pasha, G. Thirupathi, *Angew. Chem., Int. Ed.*, 2017, **56**, 12930–12934.
4) Z.-J. Jia, H. Jiang, J.-L. Li, B. Gschwend, Q.-Z. Li, X. Yin, J. Grouleff, Y.-C. Chen and K. A. Jørgensen, *J. Am. Chem. Soc*., 2011, **133**, 5053–5061.
5) O. Lozano, G. Blessley, T. M. D Campo, A. L. Thompson, G. T. Giuffredi, M. Bettati, M. Walker, R. Borman, V. R. Gouverneur, *Angew. Chem*., 2011, **123**, 8255-8259

NMR Experiment

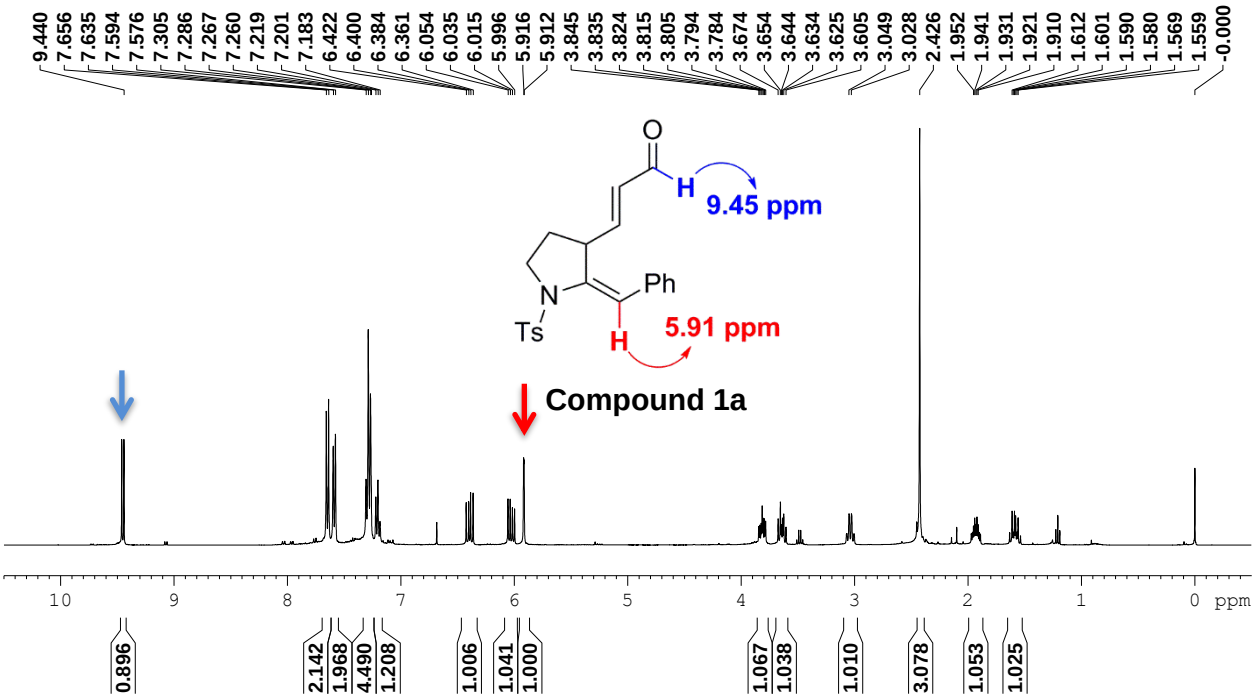


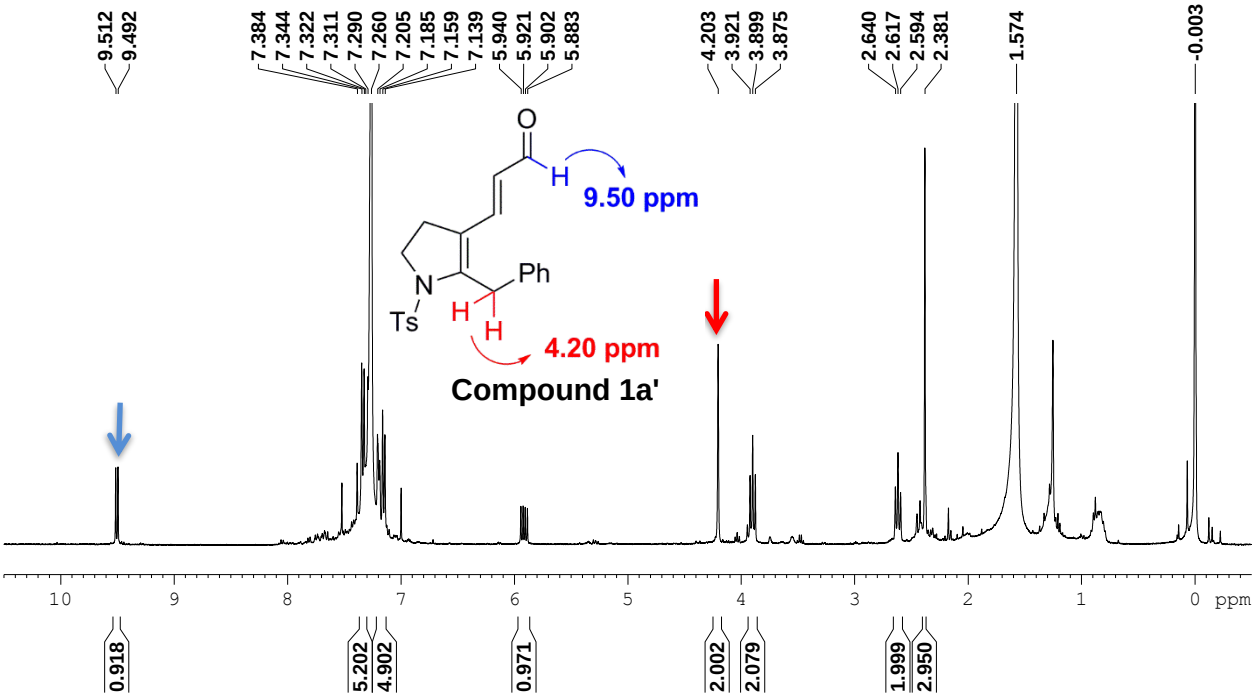
1a **1a'**

^{1}H NMR spectra of intermediate formation (10-9 ppm)

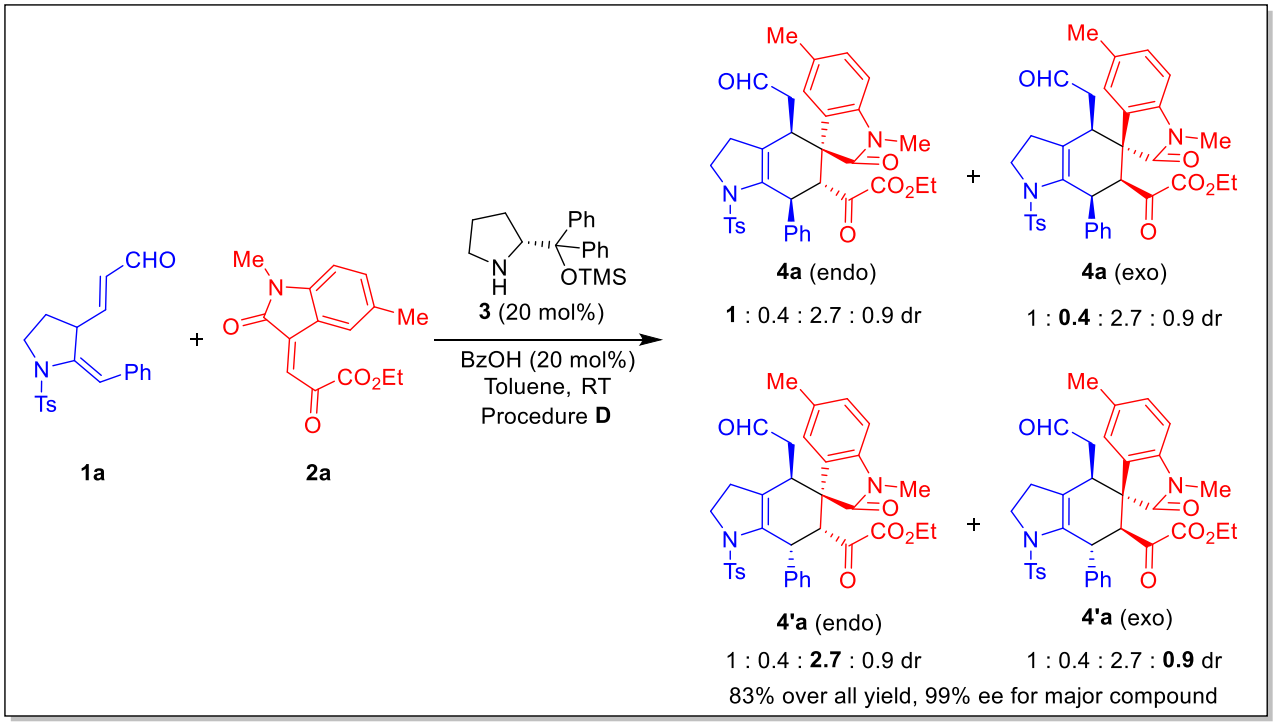


^{1}H NMR Spectra of compound 1a and compound 1a' (10.5-0 ppm)

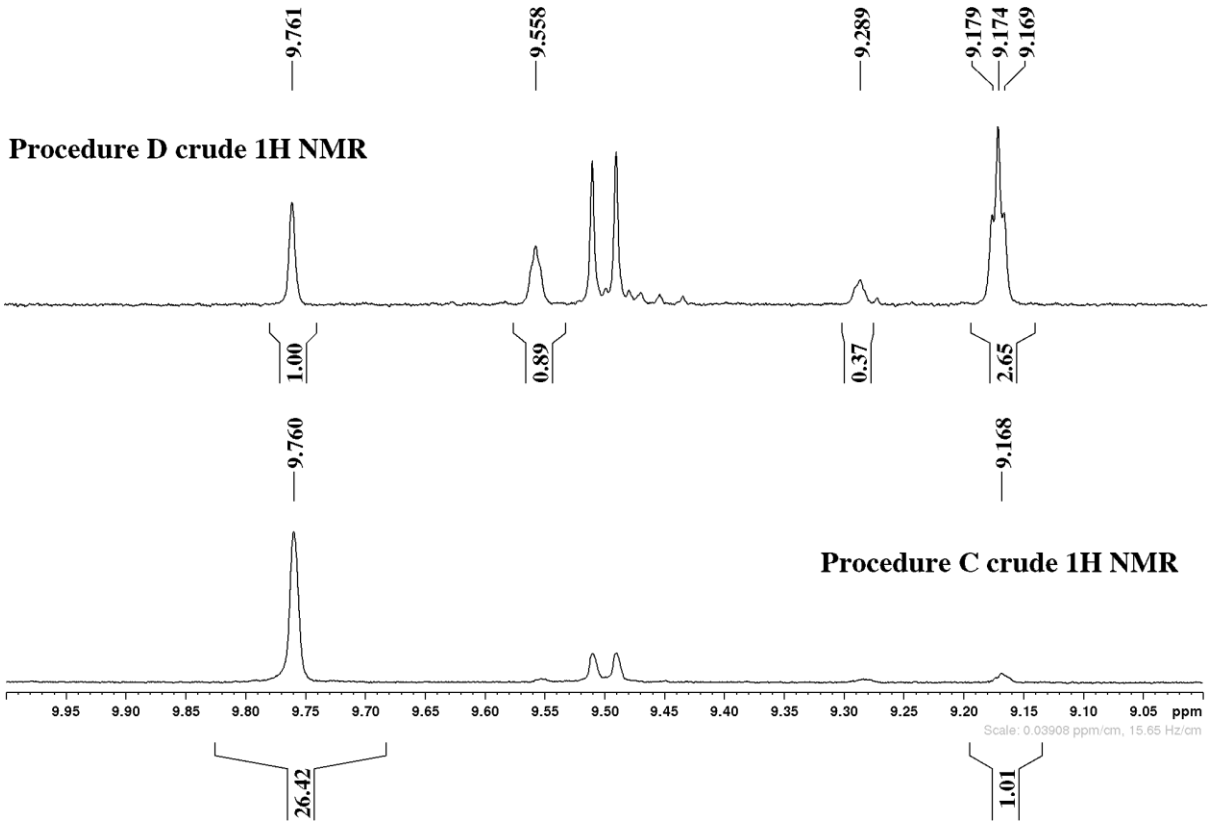




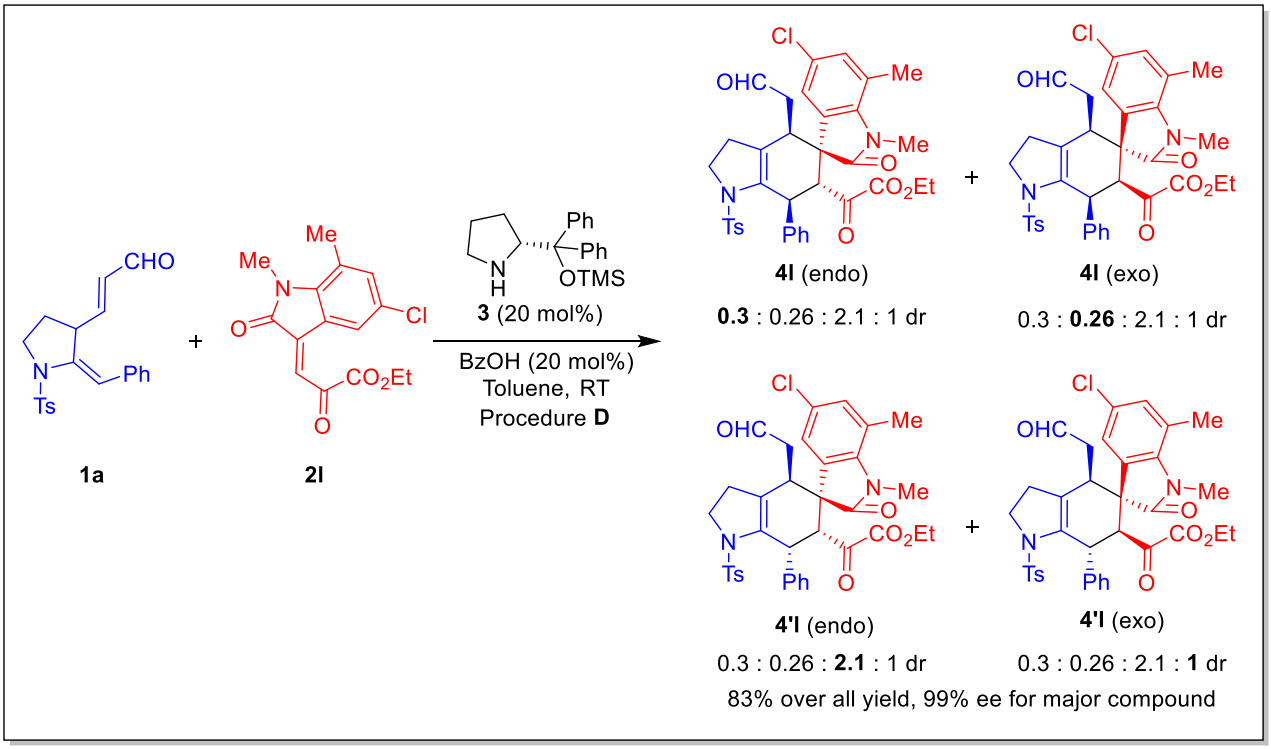
Scheme-1



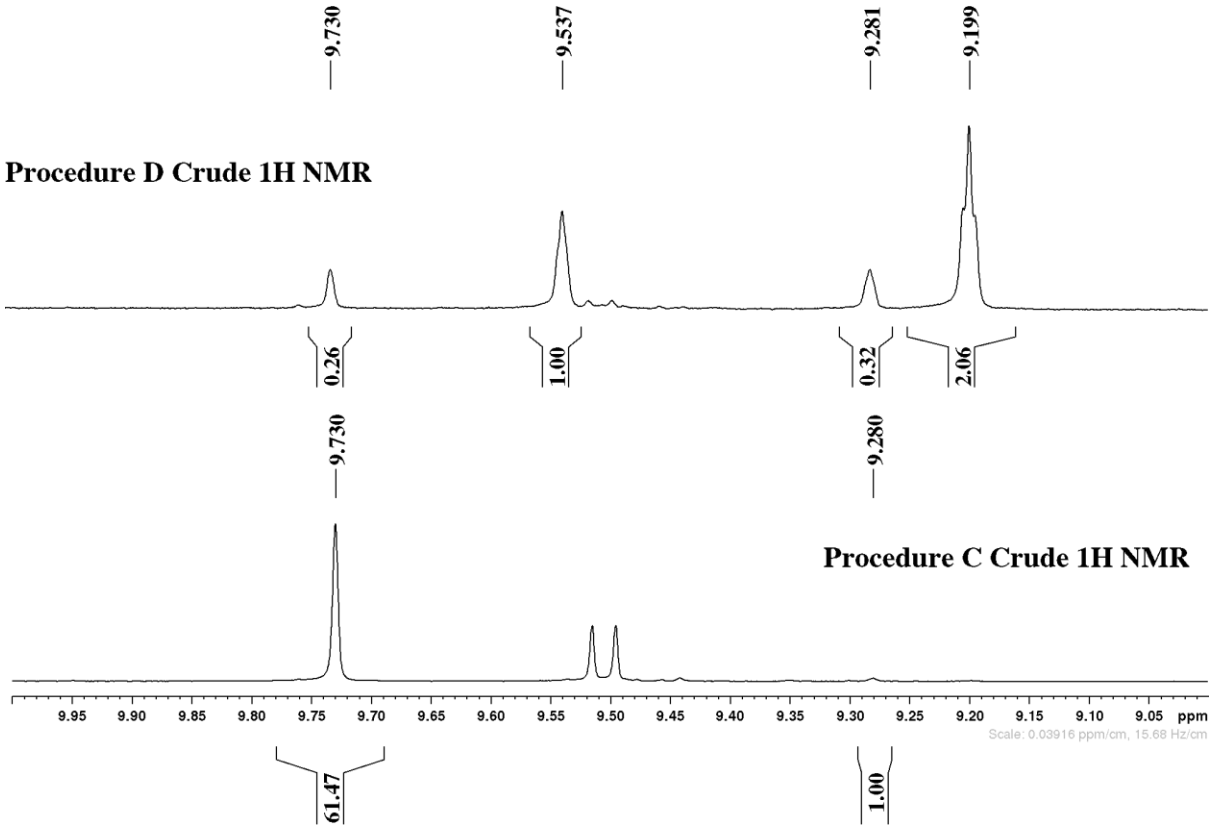
Selectivity comparison using ^{1}H NMR analysis (10-9 ppm)



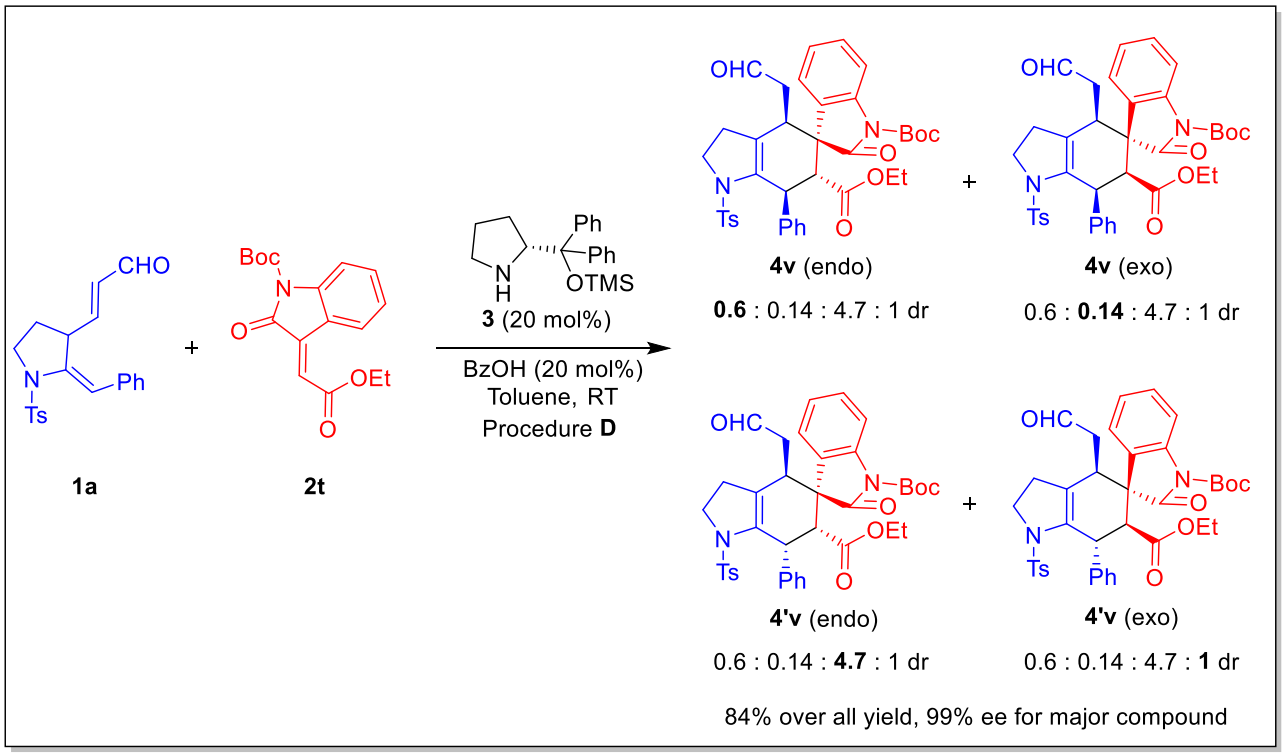
Scheme-2



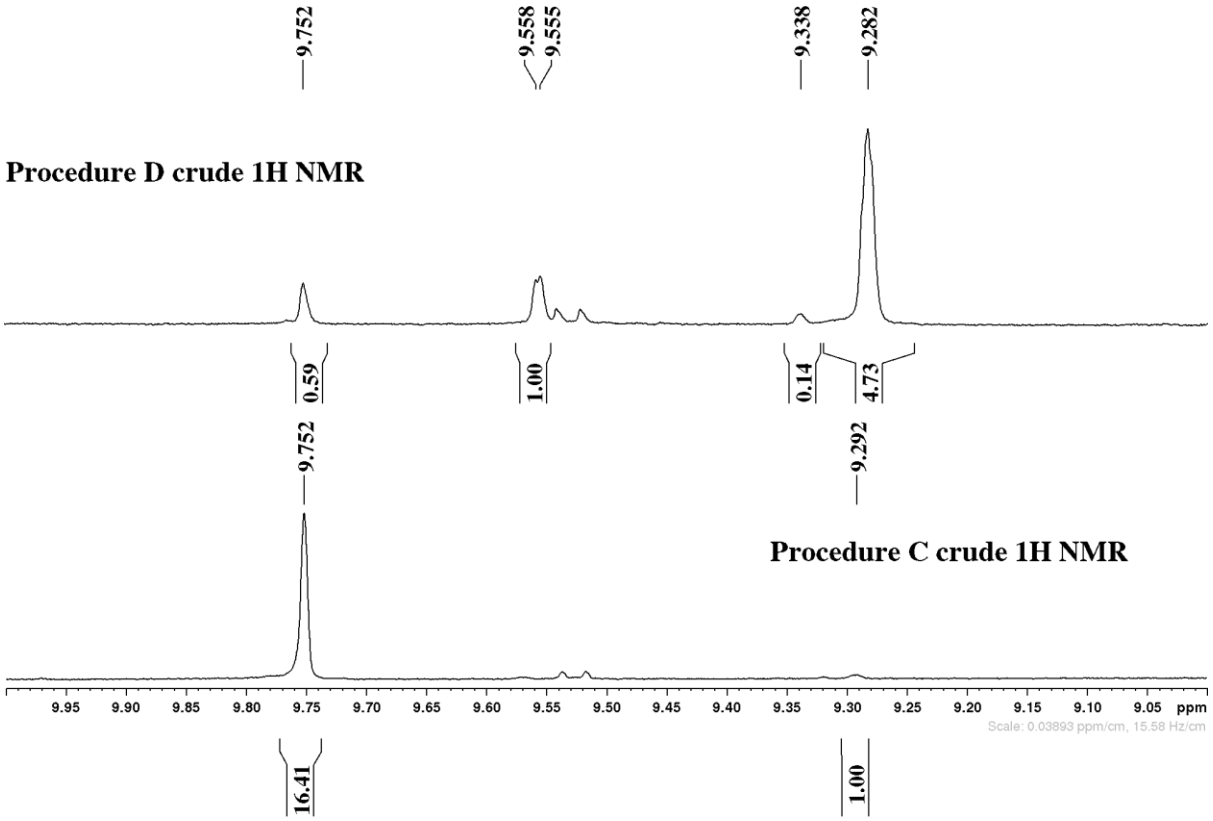
Selectivity comparison using ^{1}H NMR analysis (10-9 ppm)

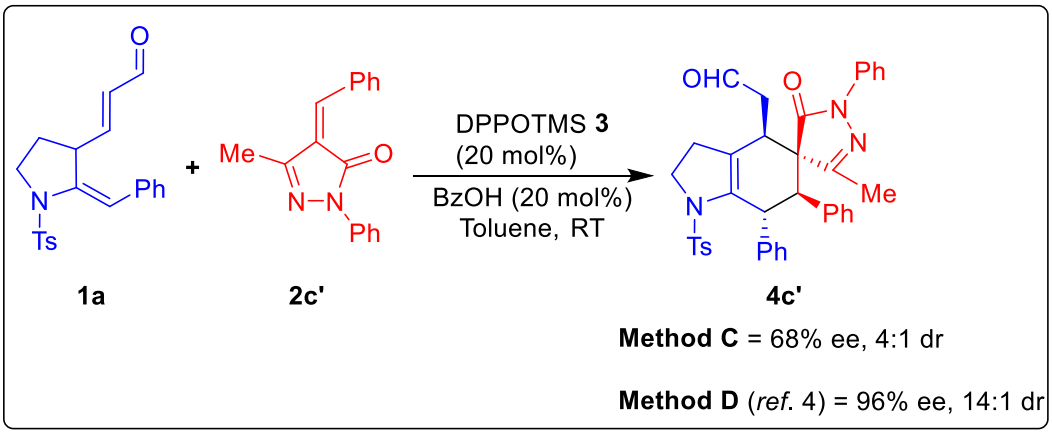


Scheme-3

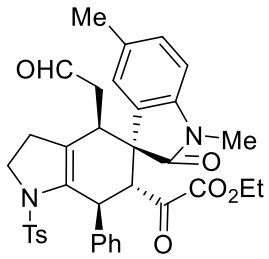


Selectivity comparison using ^{1}H NMR analysis (10-9 ppm)





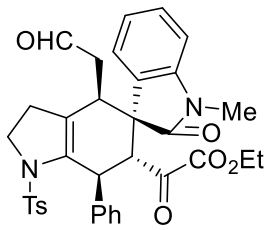
ethyl 2-((4R,5R,6R,7S)-1',5'-dimethyl-2'-oxo-4-(2-oxoethyl)-7-phenyl-1-tosyl-1,2,3,4,6,7-hexahydrospiro[indole-5,3'-indolin]-6-yl)-2-oxoacetate (4a):



4a

Prepared by following general procedure **C** purified by column chromatography using EtOAc/hexane and isolated product **4a** in 78% yield as a pale yellow solid with M. P. 154 - 158 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IA column (hexane/EtOAc = 73:27, flow rate 0.4 mL/min, λ = 254 nm), t_R = 23.625 min (major), t_R = 28.831 min (minor), **$[\alpha]_D^{25}$ = +241.64 ($CHCl_3$, *c* = 0.277 g/100mL, $CHCl_3$ for 99% *ee*)**; IR (neat) ν_{max} 2926, 1716, 1618, 1151, 1091 and 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.76 (1H, s), 7.54 (1H, s), 7.23 – 7.20 (3H, m), 7.18 (1H, d, *J* = 7.9 Hz), 7.11 - 7.09 (2H, m), 7.06 – 6.99 (4H, m), 6.77 (1H, d, *J* = *7.9 Hz*), 4.62 - 4.59 (1H, m), 4.29 (1H, d, *J* = 10.9 Hz), 4.14 - 4.08 (1H, m), 3.95 - 3.82 (2H, m), 3.74 (1H, dd, *J* = 9.6, 9.3 Hz), 3.37 (1H, dq, *J* = 2.3, 11.6 Hz), 3.12 (1H, d, *J*= *10.2 Hz*), 3.06 (3H, s), 2.84 - 2.74 (1H, m), 2.58 (1H, dd, *J* = 2.5, 2.5 Hz), 2.45 (3H, s), 2.39 - 2.35 (1H, m), 2.32 (3H, s), 1.09 (1H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT-135) δ 199.3 (C, H-*C*=O), 194.3 (C,*C*=O), 176.2 (C, N-*C*=O), 160.9 (C, O-*C*=O), 143.4 (C), 140.2 (C), 139.0 (C), 138.6(C), 136.7 (C), 133.6 (2C), 130.1 (C), 129.3 (2CH), 129.0 (2CH), 128.8 (2CH), 128.5 (2CH), 127.3 (2CH), 125.5 (CH), 108.3 (CH), 62.3 (CH_2), 52.3 (CH), 51.4 (C), 49.6 (CH_2), 43.8 (CH_2), 43.2 (CH), 37.9 (CH), 31.7 (CH_2), 26.3 (CH), 21.5 (CH), 21.4 (CH), 13.7 (CH); HRMS (ESI) m/z: 663.21354 $[M + Na]^+$, calcd for $C_{36}H_{36}O_7N_2NaS$; Found 663.21368.

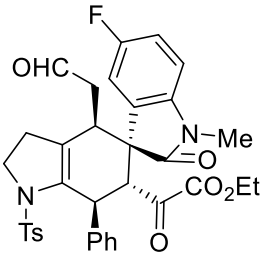
ethyl2-((4R,5R,6R,7S)-1'-methyl-2'-oxo-4-(2-oxoethyl)-7-phenyl-1-tosyl-1,2,3,4,6,7-hexahydrospiro[indole-5,3'-indolin]-6-yl)-2-oxoacetate (4b):



4b

Prepared by following general procedure **C** purified by column chromatography using EtOAc/hexane and isolated product **4b** in 78% yield as a pale yellow solid with M. P. 95 - 100 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IC column (hexane/EtOAc = 73:27, flow rate 0.5 mL/min, λ = 254 nm), t_R = 19.872 min (minor), t_R = 42.214 min (major), **$[\alpha]_D^{25}$ = +171.875 ($CHCl_3$, *c* = 1.12 g/100mL, $CHCl_3$ for 96% *ee*)**; IR (neat) ν_{max} 2926, 1697, 1610, 1157, 1089 and 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.74 (1H, s), 7.47 (1H, d, *J* = 7.5 Hz), 7.36 (1H, t, *J* = 7.8 Hz), 7.24 - 7.22 (3H, m), 7.17 - 7.15 (2H, m), 7.12 - 7.07 (5H, m), 6.88 (1H, d, *J* = 7.6 Hz), 4.57 - 4.53 (1H, m), 4.28 (1H, d, *J* = 10.8 Hz), 4.17 (1H, m), 3.90 - 3.38 (2H, m), 3.73 (1H, dd, *J* = 9.8, 9.6 Hz), 3.50 (1H, dq, *J* = 9.6, 13.6 Hz), 3.10 (1H, br s), 3.06 (3H, s), 2.74 - 2.64 (1H, m), 2.56 (1H, dd, *J* = 2.5, 2.4 Hz), 2.4 - 2.38 (1H, m), 2.36 (3H, s), 1.09 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT-135) δ 199.2 (C, H-*C*=O), 194.3 (C,*C*=O), 176.2 (C, N-*C*=O), 160.9 (C,O-*C*=O), 143.5 (C), 142.5 (C), 139.2 (C), 138.2 (C), 136.8 (C), 130.2 (C), 129.4 (2CH), 128.8 (2CH), 128.7 (2CH), 128.5 (2CH), 128.0 (C), 127.3 (2CH), 124.3 (CH),123.6 (CH), 108.6 (CH), 62.3 (CH_2), 52.5 (CH), 51.3 (C), 49.7 (CH_2), 43.7 (CH_2), 43.0 (CH), 37.8 (CH), 31.4 (CH_2), 26.3 (CH), 21.5 (CH), 13.7 (CH); HRMS (ESI) m/z: 649.19789 $[M + Na]^+$, calcd for $C_{35}H_{34}O_7N_2NaS$; Found 649.19781

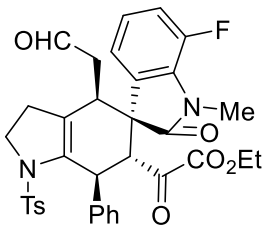
ethyl2-((4R,5R,6R,7S)-5'-fluoro-1'-methyl-2'-oxo-4-(2-oxoethyl)-7-phenyl-1-tosyl-1,2,3,4,6,7-hexahydrospiro[indole-5,3'-indolin]-6-yl)-2-oxoacetate (4c):



4c

Prepared by following general procedure **C** purified by column chromatography using EtOAc/hexane and isolated product **4c** in 78% yield as a pale yellow solid with M. P. 103 - 107 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IA column (hexane/EtOAc = 73:27, flow rate 0.5 mL/min, λ = 254 nm), t_R = 22.958 min (major), t_R = 26.401 min (minor), **$[\alpha]_D^{25}$ = +161.568 ($CHCl_3$, *c* = 0.145 g/100mL, $CHCl_3$ for 98.6% *ee*)**; IR (neat) ν_{max} 2926, 1718, 1697, 1492, 1155, 1089 and 665 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.73 (1H, s), 7.34 (1H, dd, *J* = 2.5, 2.5 Hz), 7.24 - 7.22 (5H, m), 7.10 - 7.06 (5H, m), 6.80 (1H, dd, *J* = 4.3, 4.2 Hz), 4.50 - 4.46 (1H, m), 4.30 (1H, d, *J* = 10.8 Hz), 4.15 (1H, m), 3.92 - 3.83 (2H, m), 3.72 (1H, dd, *J* = 9.7, 9.7 Hz), 3.52 (1H, dq, *J* =9.5, 13.7 Hz), 3.08 (1H, br, d, *J=9.6 Hz*), 3.05 (3H, s), 2.71 - 2.64 (1H, m), 2.57 (1H, dd, *J* =2.2, 2.2 Hz), 2.83 - 2.32 (4H, m), 1.08 (3H, t, *J* =7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT-135) δ 199.1 (C, H-*C*=O), 194.4 (C,*C*=O), 175.9 (C, N-*C*=O), 160.6 (C, C=O), 159.6 (C, *C*F, d, *J* = 239 Hz), 143.7 (C), 138.8 (C), 138.6 (C), 138.2 (C), 136.4 (C), 131.9 (C), 131.8 (C), 129.5 (2CH), 128.6 (2CH), 128.6 (2CH), 128.2 (C), 127.4 (CH), 127.3 (2CH), 115.1 (CH, d *J* = 30 Hz),112.7 (CH, d, *J* = 30 Hz), 109.0 (CH, d, *J* = 20 Hz), 62.4 (CH_2), 52.3 (CH), 51.6 (C), 49.7 (CH_2), 43.7 (CH_2), 43.1 (CH), 37.6 (CH), 31.3 (CH_2), 26.4 (CH_3), 21.5 (CH_3), 13.7 (CH_3); HRMS (ESI) m/z: 667.18847 $[M + Na]^+$, calcd for $C_{35}H_{33}O_7N_2FNaS$; Found 667.18848.

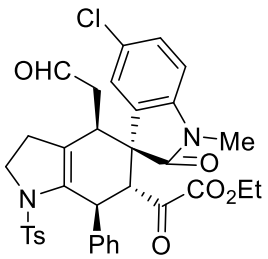
ethyl2-((4R,5R,6R,7S)-7'-fluoro-1'-methyl-2'-oxo-4-(2-oxoethyl)-7-phenyl-1-tosyl-1,2,3,4,6,7-hexahydrospiro[indole-5,3'-indolin]-6-yl)-2-oxoacetate (4d):



4d

Prepared by following general procedure **C** purified by column chromatography using EtOAc/hexane and isolated product **4d** in 78% yield as a pale yellow solid with M. P. 90 - 92 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IC column (hexane/EtOAc = 73:27, flow rate 0.5 mL/min, λ = 254 nm), t_R = 13.699 min (minor), t_R = 24.916 min (major), **$[\alpha]_D^{25}$ = +166.692 ($CHCl_3$, *c* = 0.236 g/100mL, $CHCl_3$ for 98% *ee*)**; IR (neat) ν_{max} 2924, 1705, 1629, 1157, 1086 and 665 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.73 (1H, s), 7.29 (1H, dd, *J* = 1.4, 1.4 Hz), 7.24 - 7.22 (3H, m), 7.13 - 7.05 (8H, m), 4.52 – 4.49 (1H, m), 4.28 (1H, d, *J* = *10.9 Hz*), 4.19 - 4.13 (1H, m), 3.95 – 3.82 (2H, m), 3.71 (1H, dd, *J* = 9.7, 9.7 Hz), 3.47 (1H, dq, *J* = 1.9, 11.5 Hz), 3.27 (3H, d, *J*= *2.8 Hz*), 3.09 (1H, br d, *J*= *2.8 Hz*), 2.75 - 2.65 (1H, m), 2.57 (1H, dd, *J* = 2.2, 2.2 Hz), 2.40 - 2.37 (1H, m), 2.35 (3H, s), 1.10 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT-135) δ 199.1 (C, H-*C*=O), 194.4 (C,*C*=O), 176.0 (C, N-*C*=O), 160.7 (C,O-*C*=O), 148.0 (C, *C*F, d, *J* = 240 Hz), 143.6 (C), 138.9 (C), 138.3 (C), 136.7 (C), 133.2 (C), 129.4 (2CH), 128.7 (2CH), 128.6 (2CH), 127.8 (2C), 127.4 (CH), 127.3 (2CH), 124.1 (CH), 120.1 (CH), 116.8 (CH, d, *J* = 20 Hz), 62.4 (CH_2), 52.4 (CH), 51.4 (C), 49.7 (CH_2), 43.7 (CH_2), 43.1 (CH), 37.8 (CH), 31.5 (CH), 28.9 (CH_2), 21.5 (CH_3), 13.7 (CH_3); HRMS (ESI) m/z: 667.18847 $[M + Na]^+$, calcd for $C_{35}H_{33}O_7N_2FNaS$; Found 667.18854

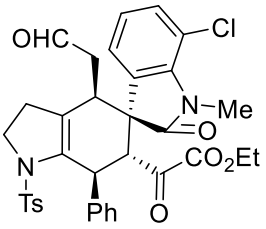
ethyl2-((4R,5R,6R,7S)-5'-chloro-1'-methyl-2'-oxo-4-(2-oxoethyl)-7-phenyl-1-tosyl-1,2,3,4,6,7-hexahydrospiro[indole-5,3'-indolin]-6-yl)-2-oxoacetate (4e):



4e

Prepared by following general procedure **C** purified by column chromatography using EtOAc/hexane and isolated product **4e** in 83% yield as a pale yellow solid with M. P. 112 - 114 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IA column (hexane/EtOAc = 73:27, flow rate 0.5 mL/min, λ = 254 nm), t_R = 22.612 min (major), t_R = 26.166 min (minor), **$[\alpha]_D^{25}$ = +228.324 ($CHCl_3$, *c* = 0.168 g/100mL, $CHCl_3$ for 99% *ee*)**; IR (neat) ν_{max} 2926, 1718, 1701, 1608, 1155, 1089 and 665 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.73 (1H, s), 7.69 (1H, d, *J* = 2 Hz), 7.37 (1H, dd, *J* = 2, 2 Hz), 7.23 - 7.15 (5H, m), 7.09 - 7.04 (4H, m), 6.81 (1H, d, *J* = 8.4 Hz), 4.52 - 4.48 (1H, m), 4.30 (1H, d, *J* = 10.9 Hz), 4.15 - 4.10 (1H, m), 3.91 - 3.79 (2H, m), 3.71 (1H, dd, *J* = 9.7, 9.7 Hz), 3.44 (1H, dq, *J* = 2.4, 11.7 Hz), 3.11 - 3.09 (1H, br m), 3.05 (3H, s), 2.77 - 2.67 (1H, m), 2.59 (1H, dd, *J* = 2.2, 2.2 Hz), 2.37 - 2.30 (4H, m), 1.08 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT-135) δ 199.1 (C, H-*C*=O), 194.4 (C,*C*=O), 176.1 (C, N-*C*=O), 160.6 (C,O-*C*=O), 143.6 (C), 141.3 (C), 138.6 (2C), 136.4 (C), 132.1 (C), 129.4 (2CH), 129.0 (C), 128.7 (2CH), 128.7 (C), 128.5 (2CH), 127.4 (2CH), 127.4 (2CH),124.9 (CH), 109.5 (CH), 62.4 (CH_2), 52.1 (CH), 51.4 (C), 49.7 (CH_2), 43.7 (CH_2), 43.3 (CH), 37.7 (CH), 31.5 (CH_2), 26.4 (CH), 21.5 (CH), 13.7 (CH); HRMS (ESI) m/z: 683.15892 $[M + Na]^+$, calcd for $C_{35}H_{33}O_7N_2ClNaS$; Found 683.15845.

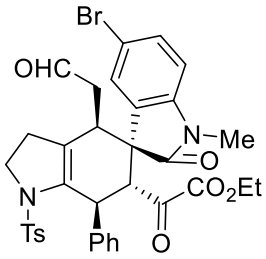
ethyl2-((4R,5R,6R,7S)-7'-chloro-1'-methyl-2'-oxo-4-(2-oxoethyl)-7-phenyl-1-tosyl-1,2,3,4,6,7-hexahydrospiro[indole-5,3'-indolin]-6-yl)-2-oxoacetate (4f):



4f

Prepared by following general procedure **C** purified by column chromatography using EtOAc/hexane and isolated product **4f** in 83% yield as a pale yellow solid with M. P. 86 - 90 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IC column (hexane/EtOAc = 73:27, flow rate 0.5 mL/min, λ = 254 nm), t_R = 13.529 min (minor), t_R = 27.343 min (major), **$[\alpha]_D^{25}$ = +146.903 ($CHCl_3$, *c* = 0.141 g/100mL, $CHCl_3$ for 98% *ee*)**; IR (neat) ν_{max} 2926, 1712, 1705, 1600, 1157, 1089 and 665 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.72 (1H, s), 7.41 (1H, d, *J* = 7.4 Hz), 7.29 (1H, d, *J* = 8.2 Hz), 7.24 – 7.22 (3H, m), 7.13 - 7.04 (7H, m), 4.51 - 4.48 (1H, m), 4.29 (1H, d, *J* = 10.9 Hz), 4.19 - 4.14 (1H, m), 3.95 - 3.82 (2H, m), 3.73 – 3.66 (1H, m), 3.52 – 3.46 (1H, m), 3.42 (3H, s), 3.06 (1H, d, *J*= 9.5 *Hz*), 2.74 - 2.64 (1H, m), 2.57 (1H, dd, *J* = 2.0, 2.0 Hz), 2.39 - 2.37 (1H, m), 2.35 (3H, s), 1.10 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT-135) δ 199.1 (C, H-*C*=O), 194.4 (C,*C*=O), 176.8 (C, N-*C*=O), 160.7 (C, O-*C*=O), 143.6 (C), 138.8 (C), 138.6 (C), 138.3 (C), 136.7 (C), 133.2 (C), 131.2 (CH), 129.4 (2CH), 128.7 (2CH), 128.6 (2CH), 127.9 (C), 127.4 (CH), 127.2 (2CH), 124.3 (CH), 122.7 (CH), 116.1 (C), 62.4 (CH_2), 52.5 (CH), 50.8 (C), 49.7 (CH_2), 43.8 (CH_2), 43.0 (CH), 38.0 (CH), 31.5 (CH_2), 29.9 (CH), 21.5 (CH), 13.7 (CH); HRMS (ESI) m/z: 683.15892 $[M + Na]^+$, calcd for $C_{35}H_{33}O_7N_2ClNaS$; Found 683.15924.

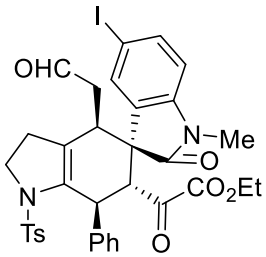
ethyl2-((4R,5R,6R,7S)-5'-bromo-1'-methyl-2'-oxo-4-(2-oxoethyl)-7-phenyl-1-tosyl-1,2,3,4,6,7-hexahydrospiro[indole-5,3'-indolin]-6-yl)-2-oxoacetate (4g):



4g

Prepared by following general procedure **C** purified by column chromatography using EtOAc/hexane and isolated product **4g** in 79% yield as a pale yellow solid with M. P. 109 - 112 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IA column (hexane/EtOAc = 73:27, flow rate 0.5 mL/min, λ = 254 nm), t_R = 22.413 min (major), t_R = 27.808 min (minor), **$[\alpha]_D^{25}$ = +185.309 ($CHCl_3$, *c* = 0.118 g/100mL, $CHCl_3$ for 98.6% *ee*)**; IR (neat) ν_{max} 2926, 1718, 1701, 1608, 1155, 1089 and 665 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.73 (1H, s), 7.84 (1H, d, *J* = 1.8 Hz), 7.52 (1H, dd, *J* = 1.8, 1.8 Hz), 7.23 - 7.19 (3H, m), 7.17 - 7.13 (2H, m), 7.11 - 7.07 (2H, m), 7.04 - 7.02 (2H, m), 6.77 (1H, d, *J* = *8.3* Hz), 4.52 - 4.48 (1H, m), 4.29 (1H, d, *J* = 11 Hz), 4.15 - 4.10 (1H, m), 3.91 - 3.79 (2H, m), 3.71 (1H, dd, *J* = 9.7, 9.7 Hz), 3.41 (1H, dq, *J* = 2.4, 11.7 Hz), 3.12 - 3.10 (1H, m), 3.05 (3H, s), 2.80 - 2.70 (1H, s), 2.59 (1H, dd, *J* = 2.2, 2.2 Hz), 2.37 - 2.31 (4H, s), 1.08 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT-135) δ 199.1 (C, H-*C*=O), 194.4 (C,*C*=O), 176.01 (C, N-*C*=O), 160.5 (C,O-*C*=O), 143.5 (C), 141.8 (C), 138.7 (C), 138.5 (C), 136.4 (C), 132.5 (C), 131.7 (CH), 129.4 (2CH), 128.9 (C), 128.8 (2CH), 128.5 (2CH), 127.5 (CH), 127.5 (CH), 127.4 (2CH), 116.5 (C), 109.9 (CH), 62.4 (CH_2), 52.1 (CH), 51.4 (C), 49.7 (CH_2), 43.6 (CH_2), 43.4 (CH), 37.7 (CH), 31.6 (CH_2), 26.4 (CH), 21.5 (CH), 13.7 (CH); HRMS (ESI) m/z: 727.10841 $[M + Na]^+$, calcd for $C_{35}H_{33}O_7N_2BrNaS$; Found 683.15845

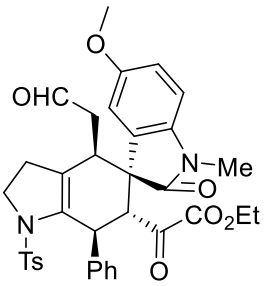
ethyl2-((4R,5R,6R,7S)-5'-iodo-1'-methyl-2'-oxo-4-(2-oxoethyl)-7-phenyl-1-tosyl-1,2,3,4,6,7-hexahydrospiro[indole-5,3'-indolin]-6-yl)-2-oxoacetate (4h):



4h

Prepared by following general procedure **C** purified by column chromatography using EtOAc/hexane and isolated product **4h** in 76% yield as a pale yellow solid with M. P. 110 - 114 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IA column (hexane/EtOAc = 73:27, flow rate 0.5 mL/min, λ = 254 nm), t_R = 22.719 min (major), t_R = 28.970 min (minor), **$[\alpha]_D^{25}$ = +223.143 ($CHCl_3$, *c* = 0.159 g/100mL, $CHCl_3$ for 99% *ee*)**; IR (neat) ν_{max} 2949, 1701, 1701, 1602, 1155, 1089 and 665 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.73 (1H, s), 8.01 (1H, d, *J* = 1.5 Hz), 7.72 (1H, dd, *J* = 1.6, 1.6 Hz), 7.27 - 7.21 (3H, m), 7.11 - 7.08 (4H, m), 7.03 - 7.01 (2H, m), 6.67 (1H, d, *J* = *8.2* Hz), 4.52 - 4.48 (1H, m), 4.28 (1H, d, *J* = 11 Hz), 4.15 - 4.10 (1H, m), 3.90 - 3.78 (2H, m), 3.71 (1H, dd, *J* = 9.7, 9.7 Hz), 3.38 (1H, dq, *J* = 2.4, 11.7 Hz), 3.12 - 3.10 (1H, m), 3.05 (3H, s), 2.84 - 2.74 (1H, m), 2.59 (1H, dd, *J* = 2.3, 2.2 Hz), 2.37 - 2.33 (1H, m), 2.32 (3H, s), 1.08 (1H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT-135) δ 199.1 (C, H-*C*=O), 194.4 (C,*C*=O), 175.9 (C, N-*C*=O), 160.6 (C,O-*C*=O), 143.5 (C), 142.4 (C), 138.7(C), 138.5 (C), 137.7 (CH), 136.5 (C), 133.0 (C), 132.7 (C), 129.3 (2CH), 129.0 (C), 128.8 (2CH), 128.5 (2CH), 127.5 (CH), 127.4 (2CH), 110.5 (CH), 86.6 (C), 62.4 (CH_2), 52.0 (CH), 51.3 (C), 49.7 (CH_2), 43.6 (CH_2), 43.4 (CH), 37.7 (CH), 31.7 (CH_2), 26.4 (CH), 21.5 (CH), 13.7 (CH); HRMS (ESI) m/z: 775.09454 $[M + Na]^+$, calcd for $C_{35}H_{33}O_7N_2IS$; Found 775.09448.

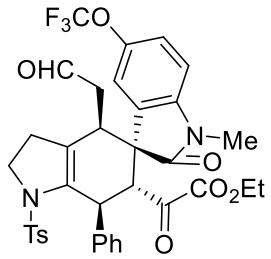
ethyl2-((4R,5R,6R,7S)-5'-methoxy-1'-methyl-2'-oxo-4-(2-oxoethyl)-7-phenyl-1-tosyl-1,2,3,4,6,7-hexahydrospiro[indole-5,3'-indolin]-6-yl)-2-oxoacetate (4i):



4i

Prepared by following general procedure **C** purified by column chromatography using EtOAc/hexane and isolated product **4i** in 82% yield as a pale yellow solid with M. P. 101 - 104 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IA column (hexane/EtOAc = 73:27, flow rate 0.5 mL/min, λ = 254 nm), t_R = 21.415 min (major), t_R = 26.059 min (minor), **$[\alpha]_D^{25}$ = +171.875 ($CHCl_3$, *c* = 0.145 g/100mL, $CHCl_3$ for 99% *ee*)**; IR (neat) ν_{max} 2926, 1718, 1693, 1598, 1153, 1089 and 663 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.75 (1H, s), 7.30 (1H, d, *J* = 2.4 Hz), 7.25 - 7.24 (3H, m), 7.15 - 7.13 (2H, m), 7.01 (4H, s), 6.93 (1H, dd, *J* = *2.4, 2.4* Hz), 6.79(1H, d, *J* = *8.6 Hz),* 4.67 - 4.64 (1H, m), 4.31 (1H, d, *J* = 11 Hz), 4.10 - 4.05 (1H, m), 3.94 - 3.84 (5H, m), 3.78 - 3.74 (1H, m), 3.36(1H, dq, *J* = 2.4, 9.3 Hz), 3.15 - 3.13 (1H, m), 3.05 (3H, s), 2.87 - 2.72 (1H, m), 2.58 (1H, dd, *J* = 2.3, 2.3 Hz), 2.38 - 2.34 (1H, m), 2.32 (3H, s), 1.10 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT-135) δ 199.2 (C, H-*C*=O), 194.4 (C,*C*=O), 175.8 (C, N-*C*=O), 160.9 (C,O-*C*=O), 156.7 (C), 143.5 (C), 139.0 (C), 138.6(C), 138.5 (C), 135.9 (C), 129.3 (2CH), 129.0 (2CH), 128.8 (C), 128.5 (2CH), 127.4 (CH), 127.3 (2CH), 114.9 (CH), 110.1 (CH), 109.2 (CH), 62.3 (CH_2), 56.4 (CH), 52.2 (CH), 51.8 (C), 49.7 (CH_2), 43.8 (CH_2), 43.2 (CH), 37.9 (CH), 31.7 (CH_2), 26.4 (CH), 21.5 (CH), 13.7 (CH); HRMS (ESI) m/z: 679.20846 $[M + Na]^+$, calcd for $C_{36}H_{36}O_8N_2S$; Found 679.20911.

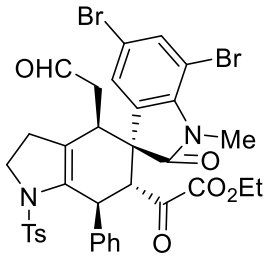
ethyl2-((4R,5R,6R,7S)-1'-methyl-2'-oxo-4-(2-oxoethyl)-7-phenyl-1-tosyl-5'-(trifluoromethoxy)-1,2,3,4,6,7-hexahydrospiro[indole-5,3'-indolin]-6-yl)-2-oxoacetate (4j):



4j

Prepared by following general procedure **C** purified by column chromatography using EtOAc/hexane and isolated product **4j** in 80% yield as a pale yellow solid with M. P. 92 - 94 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IA column (hexane/EtOAc = 73:27, flow rate 0.5 mL/min, λ = 254 nm), t_R = 16.404 min (major), t_R = 18.519 min (minor), **$[\alpha]_D^{25}$ = +161.15 ($CHCl_3$, *c* = 0.182 g/100mL, $CHCl_3$ for 98% *ee*)**; IR (neat) ν_{max} 2926, 1716, 1618, 1151, 1091 and 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.74 (1H, s), 7.57 (1H, d, *J* = 1.3 Hz), 7.29 - 7.28 (1H, m), 7.23 - 7.20 (3H, m), 7.09 - 7.07 (4H, m), 7.02 - 7.00 (2H, m), 6.87 (1H, d, *J* = *8.5 Hz*), 4.51 - 4.48 (1H, m), 4.32 (1H, d, *J* = 11 Hz), 4.18 - 4.12 (1H, m), 3.92 - 3.80 (2H, m), 3.72 (1H, dd, *J* = 9.7, 9.6 Hz), 3.44(1H, dq, *J* = 2.1, 9.4 Hz), 3.10 (1H, br d, *J*= *9.6 Hz*), 3.07 (3H, s), 2.76 - 2.66 (1H, m), 2.59 (1H, dd, *J* = 2.3, 2.2 Hz), 2.39 - 2.35 (1H, m), 2.34 (3H, s), 1.08 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT-135) δ 199.1 (C, H-*C*=O), 194.4 (C,*C*=O), 176.3 (C, N-*C*=O), 160.5 (C,O-*C*=O), 145.3 (C), 143.5 (C), 141.3 (C), 138.7(C), 138.5 (C), 136.5 (C), 131.9 (C), 129.3 (2CH), 128.7 (2CH), 128.6 (2CH), 127.9 (C), 127.4 (CH), 127.2 (2CH), 120.6 (C, CF_3, q, *J* = 260 Hz), 118.7 (CH), 108.9 (CH), 62.4 (CH_2), 52.1 (CH), 51.5 (C), 49.6 (CH_2), 43.7 (CH_2), 43.2 (CH), 37.7 (CH), 31.6 (CH_2), 26.5 (CH_3), 21.4 (CH_3), 13.7 (CH_3); HRMS (ESI) m/z:733.18019 $[M + Na]^+$, calcd for $C_{36}H_{33}O_8N_2F_3S$; Found 733.18018.

ethyl 2-((4R,5R,6R,7S)-5',7'-dibromo-1'-methyl-2'-oxo-4-(2-oxoethyl)-7-phenyl-1-tosyl-1,2,3,4,6,7-hexahydrospiro[indole-5,3'-indolin]-6-yl)-2-oxoacetate (4k):

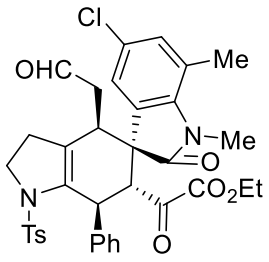


4k

Prepared by following general procedure **C** purified by column chromatography using EtOAc/hexane and isolated product **4k** in 72% yield as a pale yellow solid with M. P. 90 - 92 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IC column (Hexane/EtOAc/IPA = 75:12.5:12.5, flow rate 0.5 mL/min, λ = 254 nm), t_R = 12.754 min (minor), t_R = 41.335 min (major), **$[\alpha]_D^{25}$ = +156.514 ($CHCl_3$, *c* = 0.159 g/100mL, $CHCl_3$ for 97% *ee*)**; IR (neat) ν_{max} 2920, 1716, 1705, 1595, 1456, 1157 and 665 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.72 (1H, s), 7.79 (1H, d, *J* = 1.8 Hz), 7.68 (1H, d, *J* = 1.8 Hz), 7.23 – 7.22 (3H, m), 7.12 - 7.06 (4H, m), 7.03 – 7.01 (2H, m), 4.46 - 4.43 (1H, m), 4.31 (1H, d, *J* = 11.1 Hz), 4.15 - 4.10 (1H, m), 3.90 - 3.78 (2H, m), 3.68 (1H, dd, *J*= 9.8, 9.8 *Hz*), 3.42 (3H, s), 3.41 – 3.35 (1H, m), 3.09 (1H, d, *J* = 9.4 Hz), 2.81 – 2.71 (1H, m), 2.60 (1H, dd, *J* = 2.1, 2.1 Hz), 2.37 - 2.35 (1H, m), 2.32 (3H, s), 1.08 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT-135) δ 198.9 (C, H-*C*=O), 194.5 (C,*C*=O), 176.8 (C, N-*C*=O), 160.3 (C, O-*C*=O), 143.6 (C), 139.4 (C), 138.7 (C), 138.2 (C), 136.5 (CH), 136.3 (C), 135.2 (C), 129.4 (2CH), 128.9 (C), 128.8 (2CH), 128.6 (2CH), 127.6 (CH), 127.4 (2CH), 126.4 (CH), 116.6 (C), 103.3 (C), 62.5 (CH_2), 52.1 (CH),

50.9 (C), 49.7 (CH_2), 43.7 (CH_2), 43.3 (CH), 37.9 (CH), 31.7 (CH_2), 30.2 (CH), 21.5 (CH), 13.7 (CH); HRMS (ESI) m/z: 807.01687 $[M + Na]^+$, calcd for $C_{35}H_{32}O_7N_2BrBr^{81}NaS$; Found 807.01617.

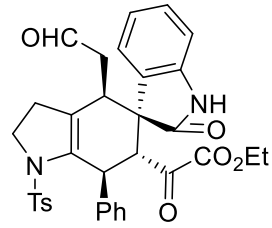
ethyl 2-((4R,5R,6R,7S)-5'-chloro-1',7'-dimethyl-2'-oxo-4-(2-oxoethyl)-7-phenyl-1-tosyl-1,2,3,4,6,7-hexahydrospiro[indole-5,3'-indolin]-6-yl)-2-oxoacetate (4l):



4l

Prepared by following general procedure **C** purified by column chromatography using EtOAc/hexane and isolated product **4l** in 95% yield as a pale yellow solid with M. P. 179 - 181 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IC column (hexane/EtOAc = 67:33, flow rate 0.5 mL/min, λ = 254 nm), t_R = 11.550 min (minor), t_R = 21.605 min (major), **$[\alpha]_D^{25}$ = +280.893 ($CHCl_3$, *c* = 0.255 g/100mL, $CHCl_3$ for 97% *ee*)**; IR (neat) ν_{max} 2931, 1743, 1714, 1597, 1157, 1089 and 657 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.72 (1H, s), 7.52 (1H, d, *J* = 1.8 Hz), 7.22 – 7.21 (3H, m), 7.19 - 7.17 (2H, m), 7.12 – 7.11 (1H, m), 7.09 – 7.04 (4H, m), 4.51 - 4.48 (1H, m), 4.27 (1H, d, *J* = 11 Hz), 4.14 - 4.09 (1H, m), 3.93 - 3.83 (2H, m), 3.69 (1H, dd, *J* = 9.8, 9.8 Hz), 3.43 (1H, dq, *J* = 2.2, 11.6 Hz), 3.30 (3H, s), 3.07 (1H, d, *J*= 9.6 *Hz*), 2.74 - 2.64 (1H, m), 2.59 – 2.55 (4H, m), 2.35 - 2.29 (4H, m), 1.08 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT-135) δ 199.1 (C, H-*C*=O), 194.4 (C,*C*=O), 176.8 (C, N-*C*=O), 160.6 (C, O-*C*=O), 143.5 (C), 139.1 (C), 138.7 (C), 138.6(C), 136.4 (C), 132.7 (C), 132.2 (CH), 129.4 (2CH), 128.8 (2CH), 128.6 (C), 128.5 (C), 128.5 (2CH), 127.4 (3CH), 122.4 (CH), 121.4 (C), 62.3 (CH_2), 52.4 (CH), 50.7 (C), 49.7 (CH_2), 43.8 (CH_2), 43.1 (CH), 38.0 (CH), 31.7 (CH_2), 29.8 (CH), 21.5 (CH), 19.2 (CH), 13.7 (CH); HRMS (ESI) m/z: 697.17457 $[M + Na]^+$, calcd for $C_{36}H_{35}O_7N_2ClNaS$; Found 697.17502.

ethyl2-oxo-2-((4R,5R,6R,7S)-2'-oxo-4-(2-oxoethyl)-7-phenyl-1-tosyl-1,2,3,4,6,7-hexahydrospiro[indole-5,3'-indolin]-6-yl)acetate (4m):

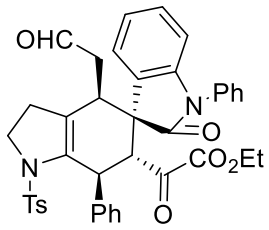


4m

Following general procedure C, prepared by column chromatography using EtOAc/hexane and isolated product **4m** in 79% yield as a pale yellow solid with M. P. 130 - 135 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IA column (hexane/EtOAc = 70:30, flow rate 0.5 mL/min, λ = 254 nm), t_R = 11.273 min (minor), t_R = 11.981 min (major), **$[\alpha]_D^{25}$ = +130.308 ($CHCl_3$, *c* = 0.295 g/100mL, $CHCl_3$ for 97% *ee*)**; IR (neat) ν_{max} 3278, 2926, 1714, 1705, 1620, 1155, 1091 and 665 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.74 (1H, s), 8.01 (1H,s), 7.44 (1H, d, *J* = 7.6 Hz), 7.25 - 7.22 (4H, m), 7.1 - 7.15 (3H, m), 7.11 - 7.07 (4H, m), 6.86 (1H, d, *J* = *7.7* Hz), 4.55 - 4.51 (1H, m), 4.31 (1H, d, *J* = 10.8 Hz), 4.19 - 4.13 (1H, m), 3.92 - 3.80 (2H, m), 3.69 (1H, dd, *J* = 9.5, 9.5 Hz), 3.50 (1H, dq, *J* = 1.8, 11.4 Hz), 3.14 (1H, d, *J* = 9.1Hz), 2.74 - 2.64 (1H, m), 2.59 (1H, dd, *J* = 2.4, 2.4 Hz), 2.40 - 2.38 (1H, m), 2.35 (3H, s) 1.06 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT-135) δ 199.3 (C, H-*C*=O), 194.4 (C,*C*=O), 178.2 (C, N-*C*=O), 160.5 (C,O-*C*=O), 143.5 (C), 139.6 (C), 139.1 (C), 138.2 (C), 136.7 (C), 130.9 (C), 129.4 (2CH), 129.4 (CH), 128.7 (2CH), 128.6 (2CH), 127.9 (C), 127.4 (CH), 127.3 (2CH), 124.6 (CH), 123.5 (CH), 110.3 (CH), 62.4 (CH_2), 52.2 (CH), 51.6 (C),

49.7 (CH_2), 43.7 (CH_2), 43.3 (CH), 37.9 (CH), 31.4 (CH_2), 21.5 (CH), 13.7 (CH); HRMS (ESI) m/z: 635.18224 $[M + Na]^+$, calcd for $C_{34}H_{32}O_7N_2S$; Found 635.18420.

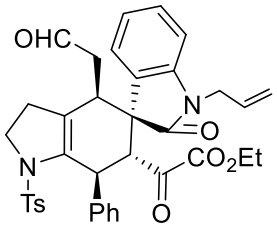
ethyl2-oxo-2-((4R,5R,6R,7S)-2'-oxo-4-(2-oxoethyl)-1',7-diphenyl-1-tosyl-1,2,3,4,6,7-hexahydrospiro[indole-5,3'-indolin]-6-yl)acetate (4n):



4n

Prepared by following general procedure **C** purified by column chromatography using EtOAc/hexane and isolated product **4n** in 72% yield as a pale yellow solid with M. P. 91 - 95 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IA column (hexane/EtOAc = 75:25, flow rate 0.5 mL/min, λ = 254 nm), t_R = 19.707 min (minor), t_R = 21.853 min (major), **$[\alpha]_D^{25}$ = +156.514 ($CHCl_3$, *c* = 0.159 g/100mL, $CHCl_3$ for 93% *ee*)**; IR (neat) ν_{max} 2924, 1712, 1610, 1155, 1091 and 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.77 (1H, s), 7.55 (1H, d, *J* = 7.3 Hz), 7.47 (1H, t, *J* = 7.3 Hz), 7.39 – 7.36 (1H, m), 7.30 - 7.28 (3H, m), 7.25 – 7.24 (3H, m), 7.17 – 7.12 (5H, m), 7.09 – 7.07 (2H, m), 6.73 (1H, d, *J* = 7.8 Hz), 4.65 - 4.61 (1H, m), 4.34 (1H, d, *J* = 10.9 Hz), 4.22 – 4.17 (1H, m), 3.81 – 3.72 (3H, m), 3.52 (1H, dq, *J*= 2.0, 11.5 *Hz*), 3.28 (1H, d, *J* = 9.8 Hz), 2.79 – 2.69 (1H, m), 2.62 (1H, dd, *J* = 1.8, 1.7 Hz), 2.44 – 2.38 (1H, m), 2.36 (3H, s), 0.97 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT-135) δ 199.4 (C, H-*C*=O), 194.5 (C,*C*=O), 176.2 (C, N-*C*=O), 160.0 (C, O-*C*=O), 143.5 (C), 143.0 (C), 139.1 (C), 138.4 (C), 136.8 (C), 133.9 (C), 130.1 (C), 129.6 (2CH), 129.4 (2CH), 128.8 (2CH), 128.7 (CH), 128.6 (2CH), 128.5 (CH), 127.9 (C), 127.4 (CH), 127.3 (2CH), 127.2 (2CH), 124.5 (CH), 123.9 (CH), 109.9 (CH), 62.3 (CH_2), 52.7 (CH), 51.3 (C), 49.8 (CH_2), 43.8 (CH_2), 43.0 (CH), 38.1 (CH), 31.5 (CH_2), 21.5 (CH), 13.5 (CH); HRMS (ESI) m/z: 711.21354 $[M + Na]^+$, calcd for $C_{40}H_{36}O_7N_2NaS$; Found 711.21283.

ethyl2-((4R,5R,6R,7S)-1'-allyl-2'-oxo-4-(2-oxoethyl)-7-phenyl-1-tosyl-1,2,3,4,6,7-hexahydrospiro[indole-5,3'-indolin]-6-yl)-2-oxoacetate (4o):

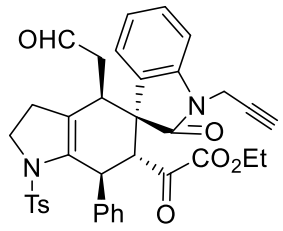


4o

Prepared by following general procedure **C** purified by column chromatography using EtOAc/hexane and isolated product **4o** in 82% yield as a pale yellow solid with M. P. 83 - 86 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IA column (hexane/EtOAc = 73:27, flow rate 0.4 mL/min, λ = 254 nm), t_R = 24.132 min (major), t_R = 27.310 min (minor), **$[\alpha]_D^{25}$ = +195.105 ($CHCl_3$, *c* = 0.173 g/100mL, $CHCl_3$ for 97% *ee*)**; IR (neat) ν_{max} 2956, 1718, 1697, 1610, 1155, 1089 and 665 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.73 (1H, s), 7.48 (1H, d, *J* = 7.4 Hz), 7.32 (1H, t, *J* = 7.7 Hz), 7.24 – 7.22 (3H, m), 7.10 - 7.06 (7H, m), 6.86 (1H, d, *J* = 7.7 Hz), 5.78 – 5.68 (1H, m), 5.23 (1H, d, *J* = 6.2 Hz), 5.20 (1H, s), 4.57 - 4.54 (1H, m), 4.32 (1H, d, *J* = 10.8 Hz), 4.28 - 4.20 (1H, m), 4.20 – 4.14 (1H, m),4.12 – 4.07 (1H, m), 3.94 – 3.82 (2H, m), 3.73 (1H, dd, *J*= 9.8, 9.8 *Hz*), 3.50 (1H, dq, *J* = 1.9, 11.5 Hz), 3.12 (1H, d, *J* = 9.4 Hz), 2.74 – 2.64 (1H, m), 2.56 (1H, dd, *J* = 2.2, 2.1 Hz), 2.39 (1H, d, *J* = 9.5 Hz), 2.35 (3H, s), 1.08 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT-135) δ 199.0 (C, H-*C*=O), 194.3 (C,*C*=O), 176.1 (C, N-*C*=O), 160.8 (C, O-*C*=O), 143.5 (C), 141.8 (C), 139.1

(C), 138.2 (C), 136.8 (C), 131.1 (CH), 130.3 (C), 129.4 (2CH), 128.6 (2CH), 128.6 (CH), 128.6 (2CH), 127.9 (C), 127.3 (CH), 127.3 (2CH), 124.3 (CH), 123.5 (CH), 117.8 (CH_2,HC=*C*H_2), 109..6 (CH), 62.3 (CH_2), 52.3 (CH), 51.2 (C), 49.7 (CH_2), 43.7 (CH_2), 43.2 (CH), 42.6 (CH_2), 37.9 (CH), 31.4 (CH_2), 21.5 (CH), 13.7 (CH); HRMS (ESI) m/z: 675.21354 $[M + Na]^+$, calcd for $C_{37}H_{36}O_7N_2NaS$; Found 675.21356.

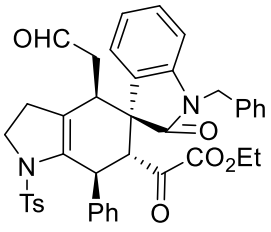
ethyl2-oxo-2-((4R,5R,6R,7S)-2'-oxo-4-(2-oxoethyl)-7-phenyl-1'-(prop-2-yn-1-yl)-1-tosyl-1,2,3,4,6,7-hexahydrospiro[indole-5,3'-indolin]-6-yl)acetate (4p):



4p

Prepared by following general procedure **C** purified by column chromatography using EtOAc/hexane and isolated product **4p** in 95% yield as a pale yellow solid with M. P. 83 - 87 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IC column (hexane/EtOAc = 75:25, flow rate 0.5 mL/min, λ = 254 nm), t_R = 19.759 min (minor), t_R = 41.009 min (major), **$[\alpha]_D^{25}$ = +225.94 ($CHCl_3$, *c* = 0.455 g/100mL, $CHCl_3$ for 96% *ee*)**; IR (neat) ν_{max} 3277, 2981, 1701, 1610, 1155 and 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.74 (1H, s), 7.49 (1H, d, *J* = 7.4 Hz), 7.38 (1H, t, *J* = 7.8 Hz), 7.24 – 7.22 (3H, m), 7.17 - 7.06 (8H, m), 4.57 – 4.53 (1H, m), 4.43 (1H, d, *J* = 2.5, 2.5 Hz), 4.30 (1H, d, *J* = 10.8 Hz),4.24 (1H, dd, *J* = 2.5, 2.5 Hz), 4.19 - 4.12 (1H, m), 3.93 - 3.81 (2H, m), 3.69 (1H, dd, *J* = 9.5, 9.5 Hz), 3.49 (1H, q, *J* = 11.4 Hz), 3.11 (1H, d, *J* = 9.1 Hz), 2.27 - 2.63 (1H, m), 2.58 (1H, dd, *J* = 2.4, 2.4 Hz), 2.40 – 2.35 (4H, m), 2.25 (1H, t, *J* = 2.5 Hz), 1.08 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT-135) δ 199.1 (C, H-*C*=O), 194.1 (C,*C*=O), 175.6 (C, N-*C*=O), 160.8 (C, O-*C*=O), 143.5 (C), 140.7 (C), 139.1 (C), 138.2 (C), 136.7 (C), 130.2 (C), 129.4 (2CH), 128.8 (2CH), 128.6 (2CH), 127.8 (C), 127.4 (2CH), 127.3 (2CH), 124.4 (CH), 123.9 (CH), 109.6 (CH), 76.3 (C≡CH), 72.5 (C≡CH), 62.3 (CH_2), 52.3 (CH), 51.3 (C), 49.7 (CH_2), 43.8 (CH_2), 43.1 (CH), 37.9 (CH), 31.4 (CH_2), 29.4 (CH_2), 21.5 (CH), 13.7 (CH); HRMS (ESI) m/z: 673.19789 $[M + Na]^+$, calcd for $C_{37}H_{34}O_7N_2NaS$; Found 673.19788.

ethyl2-((4R,5R,6R,7S)-1'-benzyl-2'-oxo-4-(2-oxoethyl)-7-phenyl-1-tosyl-1,2,3,4,6,7-hexahydrospiro[indole-5,3'-indolin]-6-yl)-2-oxoacetate (4q):

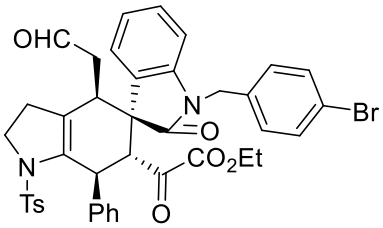


4q

Prepared by following general procedure **C** purified by column chromatography using EtOAc/hexane and isolated product **4q** in 77% yield as a pale yellow solid with M. P. 90 - 92 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IA column (hexane/EtOAc = 73:27, flow rate 0.4 mL/min, λ = 254 nm), t_R = 26.269 min (major), t_R = 31.077 min (minor), **$[\alpha]_D^{25}$ = +166.965 ($CHCl_3$, *c* = 0.255 g/100mL, $CHCl_3$ for 99% *ee*)**; IR (neat) ν_{max} 2924, 1718, 1697, 1610, 1155, 1089 and 584 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.77 (1H, s), 7.50 (1H, d, *J* = 7.3 Hz), 7.32 – 7.30 (2H, m), 7.25 - 7.19 (7H, m), 7.16 – 7.14 (2H, m), 7.12 – 7.10 (2H, m), 7.08 – 7.06 (3H, m), 6.65 (1H, d, *J* = 7.7 Hz), 4.91 (1H, d, *J* = 16 Hz), 4.63 (1H, d, *J* = 16 Hz), 4.59 – 4.55 (1H, m), 4.37 (1H, d, *J* = 10.8 Hz), 4.21 – 4.15 (1H, m), 3.93 – 3.83 (2H, m), 3.78 (1H, dd, *J* = 6.2, 9.6 Hz), 3.51 (1H, dq, *J*= 1.9, 11.5 *Hz*), 3.20 (1H, d, *J* = 9.2 Hz), 2.76 – 2.66 (1H, m), 2.60 (1H, dd, *J* = 2.2, 2.2 Hz), 2.42 – 2.38 (1H, m), 2.35

(3H, s), 1.05 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT-135) δ 199.1 (C, H-*C*=O), 194.4 (C,*C*=O), 176.5 (C, N-*C*=O), 160.8 (C, O-*C*=O), 143.5 (C), 141.8 (C), 139.1 (C), 138.2 (C), 136.8 (C), 135.0 (C), 130.2 (C), 129.4 (2CH), 128.8 (2CH), 128.7 (2CH), 128.7 (CH), 128.6 (2CH), 128.0 (C), 127.5 (CH), 127.4 (CH), 127.3 (2CH), 127.0 (2CH), 124.4 (CH), 123.6 (CH), 109.9 (CH), 62.4 (CH_2), 52.4 (CH), 51.4 (C), 49.8 (CH_2), 44.1 (CH_2), 43.8 (CH_2), 43.3 (CH), 37.9 (CH), 31.4 (CH_2), 21.5 (CH), 13.7 (CH); HRMS (ESI) m/z: 725.22919 $[M + Na]^+$, calcd for $C_{41}H_{38}O_7N_2NaS$; Found 725.22943.

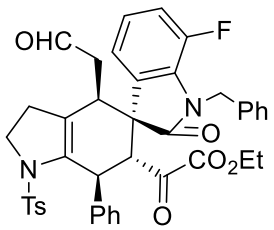
ethyl2-((4R,5R,6R,7S)-1'-(4-bromobenzyl)-2'-oxo-4-(2-oxoethyl)-7-phenyl-1-tosyl-1,2,3,4,6,7-hexahydrospiro[indole-5,3'-indolin]-6-yl)-2-oxoacetate (4r):



4r

Prepared by following general procedure **C** purified by column chromatography using EtOAc/hexane and isolated product **4r** in 95% yield as a pale yellow solid with M. P. 112 - 115 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IC column (hexane/EtOAc = 67:33, flow rate 0.5 mL/min, λ = 254 nm), t_R = 9.771 min (minor), t_R = 10.714 min (major), **$[\alpha]_D^{25}$ = +158.401 ($CHCl_3$, *c* = 0.159 g/100mL, $CHCl_3$ for 98% *ee*)**; IR (neat) ν_{max} 2922, 1720, 1699, 1610, 1157, 1089 and 665 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (1H, s), 7.51 (1H, d, *J* = 7.2 Hz), 7.25 – 7.21 (4H, m), 7.15 - 7.06 (9H, m), 6.62 (1H, d, *J* = 7.8 Hz), 4.84 (1H, d, *J* = 16.1 Hz), 4.60 – 4.54 (2H, m), 4.35 (1H, d, *J* = 10.8 Hz), 4.21 – 4.15 (1H, m), 3.92 – 3.82 (2H, m), 3.77 (1H, dd, *J* = 9.8, 9.8 Hz), 3.50 (1H, q, *J*= 9.6 *Hz*), 3.19 (1H, d, *J* = 9.5 Hz), 2.76 – 2.66 (1H, m), 2.60 (1H, dd, *J* = 1.9, 1.9 Hz), 2.42 – 2.35 (4H, m), 1.05 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT-135) δ 199.1 (C, H-*C*=O), 194.5 (C,*C*=O), 176.6 (C, N-*C*=O), 160.7 (C, O-*C*=O), 143.5 (C), 141.5 (C), 139.0 (C), 138.3 (C), 136.8 (C), 134.1 (C), 131.9 (2CH), 130.2 (C), 129.4 (2CH), 128.8 (4CH), 128.7 (CH), 128.6 (2CH), 127.9 (C), 127.4 (CH), 127.3 (2CH), 124.5 (CH), 123.8 (CH), 121.5 (C), 109.7 (CH), 62.4 (CH_2), 52.4 (CH), 51.3 (C), 49.7 (CH_2), 43.8 (CH_2), 43.5 (CH_2), 43.3 (CH), 37.8 (CH), 31.4 (CH_2), 21.5 (CH), 13.7 (CH); HRMS (ESI) m/z: 803.13971 $[M + Na]^+$, calcd for $C_{41}H_{37}O_7N_2BrNaS$; Found 803.14281.

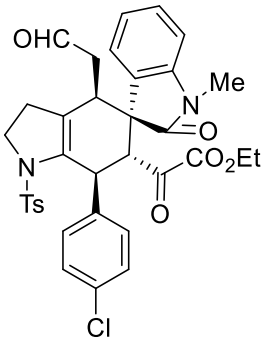
ethyl2-((4R,5R,6R,7S)-1'-benzyl-7'-fluoro-2'-oxo-4-(2-oxoethyl)-7-phenyl-1-tosyl-1,2,3,4,6,7-hexahydrospiro[indole-5,3'-indolin]-6-yl)-2-oxoacetate (4s):



4s

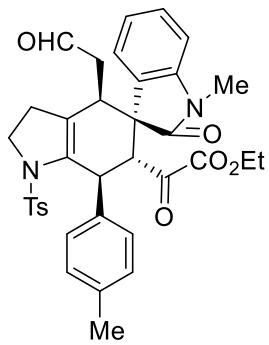
Prepared by following general procedure **C** purified by column chromatography using EtOAc/hexane and isolated product **4s** in 95% yield as a pale yellow solid with M. P. 102 - 105 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IC column (hexane/EtOAc = 67:33, flow rate 0.5 mL/min, λ = 254 nm), t_R = 9.884 min (minor), t_R = 11.192 min (major), **$[\alpha]_D^{25}$ = +177.114 ($CHCl_3$, *c* = 0.35 g/100mL, $CHCl_3$ for 97% *ee*)**; IR (neat) ν_{max} 2926, 1720, 1697, 1618, 1155, 1089 and 584 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (1H, s), 7.37 (1H, dd, *J* = 2.5, 2.5 Hz), 7.34 – 7.30 (2H, m), 7.27 - 7.26 (1H, m), 7.24 – 7.20 (7H, m), 7.10 – 7.07 (4H, m), 6.91 (1H, dt, *J* = 8.8, 8.8 Hz), 6.56 (1H, dd, *J* = 4.4, 4.3 Hz), 4.89 (1H, d, *J* = 16 Hz), 4.61 (1H, d, *J* = 16 Hz), 4.52 – 4.49 (1H, m),

4.38 (1H, d, *J* = 10.8 Hz), 4.19 – 4.13 (1H, m), 3.92 – 3.83 (2H, m), 3.77 (1H, dd, *J* = 9.6, 9.6 Hz), 3.52 (1H, dq, *J*= 2.0, 11.6 *Hz*), 3.19 (1H, d, *J* = 9.3 Hz), 2.73 – 2.58 (2H, m), 2.39 – 2.34 (4H, m), 1.05 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT-135) δ 198.9 (C, H-*C*=O), 194.5 (C,*C*=O), 176.3 (C, N-*C*=O), 160.5 (C, O-*C*=O), 159.6 (C, *C*F, d, *J* = 240 Hz), 143.7 (C), 138.8 (C), 138.2 (C), 137.8 (C), 136.4 (C), 134.7 (C), 131.8 (C), 129.6 (2CH), 128.8 (2CH), 128.7 (2CH), 128.6 (2CH), 128.3 (C), 127.7 (CH), 127.4 (CH), 127.3 (2CH), 127.0 (2CH), 115.0 (CH, d, *J* = 20 Hz), 112.7 (CH, d, *J* = 30 Hz), 110.4 (CH, d, *J* = 8 Hz), 62.4 (CH_2), 52.2 (CH), 51.6 (C), 49.8 (CH_2), 44.2 (CH_2), 43.7 (CH_2), 43.3 (CH), 37.7 (CH), 31.3 (CH_2), 21.5 (CH_3), 13.7 (CH_3); HRMS (ESI) m/z: 743.21977 $[M + Na]^+$, calcd for $C_{41}H_{37}O_7N_2FNaS$; Found 743.21950.



4t

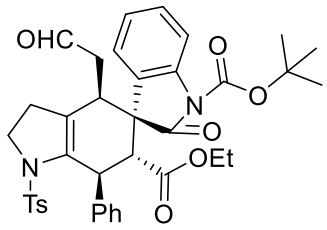
ethyl2-((4R,5R,6R,7S)-7-(4-chlorophenyl)-1'-methyl-2'-oxo-4-(2-oxoethyl)-1-tosyl-1,2,3,4,6,7-hexahydrospiro[indole-5,3'-indolin]-6-yl)-2-oxoacetate (4t): Prepared following general procedure **C** purified by column chromatography using EtOAc/hexane and isolated product **4t** in 67% yield as a pale yellow solid with M. P. 94 - 96 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IC column (hexane/EtOAc = 72:28, flow rate 0.5 mL/min, λ = 254 nm), t_R = 13.314 min (minor), t_R = 18.225 min (major), **$[\alpha]_D^{25}$ = +201.616 ($CHCl_3$, *c* = 0.332 g/100mL, $CHCl_3$ for 98% *ee*)**; IR (neat) ν_{max} 2926, 1720, 1697, 1610, 1157, 1089 and 754 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (1H, s), 7.44 (1H, d, *J* = 7.5 Hz), 7.37 (1H, d, *J* = 7.8 Hz), 7.23 – 7.21 (2H, m), 7.15 - 7.10 (5H, m), 6.99 (2H, d, *J* = 8.4 Hz), 6.87 (1H, d, *J* = 7.8 Hz), 4.55 – 4.52 (1H, m), 4.28 – 4.19 (2H, m), 4.02 – 3.88 (2H, m), 3.69 (1H, dd, *J* = 9.5, 9.6 Hz), 3.57 (1H, q, *J*= 9.7 *Hz*), 3.12 – 3.06 (4H, m), 2.73 – 2.63 (1H, m), 2.55 (1H, dd, *J* = 2.3, 2.3 Hz), 2.42 – 2.36 (4H, m), 1.12 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT-135) δ 199.1 (C, H-*C*=O), 193.9 (C,*C*=O), 175.9 (C, N-*C*=O), 161.1 (C, O-*C*=O), 143.7 (C), 142.5 (C), 137.7 (C), 137.6 (C), 136.9 (C), 133.2 (C), 130.1 (2CH), 129.8 (C), 129.5 (2CH), 128.9 (CH), 128.6 (2CH), 127.9 (C), 126.9 (2CH), 124.3 (CH), 123.6 (CH), 108.7 (CH), 62.5 (CH_2), 52.4 (CH), 51.3 (C), 49.9 (CH_2), 43.7 (CH_2), 42.1 (CH), 37.7 (CH), 31.3 (CH_2), 26.3 (CH), 21.6 (CH), 13.7 (CH); HRMS (ESI) m/z: 683.15892 $[M + Na]^+$, calcd for $C_{35}H_{33}O_7N_2ClNaS$; Found 683.16214.



4u

ethyl2-((4R,5R,6R,7S)-1'-methyl-2'-oxo-4-(2-oxoethyl)-7-(p-tolyl)-1-tosyl-1,2,3,4,6,7-hexahydrospiro[indole-5,3'-indolin]-6-yl)-2-oxoacetate (4u): Prepared by following general procedure **C** purified by column chromatography using EtOAc/hexane and isolated product **4u** in 65% yield as a pale yellow solid with M. P. 90 - 93 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IC column (hexane/EtOAc = 75:25, flow rate 0.5 mL/min, λ = 254 nm), t_R = 22.701 min (minor), t_R = 46.590 min (major), **$[\alpha]_D^{25}$ = +131.000 ($CHCl_3$, *c* = 0.1 g/100mL, $CHCl_3$ for 97% *ee*)**; IR (neat) ν_{max} 2926, 1720, 1697, 1610, 1157, 1089 and 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (1H, s), 7.45 (1H, d, *J* = 7.3 Hz), 7.38 – 7.34 (1H,

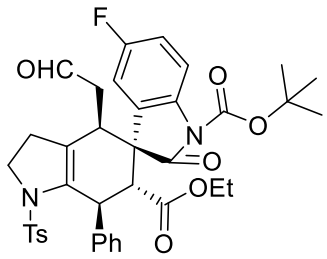
m), 7.18 (2H, d, *J* = 8.3 Hz), 7.13 - 7.11 (1H, m), 7.07 (2H, d, *J* = 8.0 Hz), 7.01 – 6.94 (4H, m), 6.88 – 6.86 (1H, m), 4.52 – 4.49 (1H, m), 4.27 (1H, d, *J* = 10.8 Hz), 4.23 – 4.18 (1H, m), 3.96 – 3.83 (2H, m), 3.72 (1H, dd, *J* = 9.6, 9.6 Hz), 3.53 (1H, q, *J*= 9.6 *Hz*), 3.08 (1H, br s), 3.06 (3H, s), 2.72 – 2.62 (1H, m), 2.55 (1H, dd, *J* = 2.4, 2.4 Hz), 2.43 – 2.37 (4H, m), 2.30 (3H, s), 1.09 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT-135) δ 199.3 (C, H-*C*=O), 194.4 (C,*C*=O), 176.2 (C, N-*C*=O), 160.9 (C, O-*C*=O), 143.3 (C), 142.5 (C), 138.4 (C), 137.0 (C), 136.9 (C), 130.3 (C), 129.3 (2CH), 129.1 (2CH), 128.7 (CH), 128.6 (2CH), 127.4 (C), 127.2 (2CH), 124.3 (CH), 123.5 (CH), 108.6 (CH), 62.3 (CH_2), 52.5 (CH), 51.3 (C), 49.8 (CH_2), 43.8 (CH_2), 42.5 (CH), 37.8 (CH), 31.4 (CH_2), 26.3 (CH), 21.5 (CH), 21.1 (CH), 13.7 (CH); HRMS (ESI) m/z: 663.21354 $[M + Na]^+$, calcd for $C_{36}H_{36}O_7N_2NaS$; Found 663.21360.



4v

1'-(tert-butyl)6-ethyl(4R,5R,6R,7S)-2'-oxo-4-(2-oxoethyl)-7-phenyl-1-tosyl-1,2,3,4,6,7-hexahydrospiro[indole-5,3'-indoline]-1',6-dicarboxylate (4v): Prepared by following general procedure **C** purified by column chromatography using EtOAc/hexane and isolated product **4v** in 73% yield as a pale yellow solid with M. P. 98 - 102 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IA column (hexane/EtOAc = 70:30, flow rate 0.5 mL/min, λ = 254 nm), t_R = 12.569 min (minor), t_R = 13.526 min (major), **$[\alpha]_D^{25}$ = +237.350 ($CHCl_3$, *c* = 0.24 g/100mL, $CHCl_3$ for 95% *ee*)**; IR (neat) ν_{max} 1728, 1350, 1249, 1149, 1022 and 586 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.73 (1H, s), 7.84 (1H, d, *J* = 8 Hz), 7.35 – 7.30 (3H, m), 7.25 – 7.21 (4H, m), 7.19 – 7.17 (2H, m), 7.16 (2H, d, *J* = 7.6 Hz), 4.85 – 4.83 (1H, m), 4.16 – 4.10 (1H, m), 3.82 – 3.70 (2H, m), 3.62 – 3.51 (2H, m), 3.34 (1H, d, *J* = 8.8 Hz), 3.08 (1H, d, *J*= 8.8 *Hz*), 2.57 – 2.48 (2H, m), 2.39 (4H, s), 1.59 (9H, s), 0.83 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT-135) δ 198.9 (C, H-*C*=O), 176.1 (C, N-*C*=O), 170.4 (C, O-*C*=O), 148.8 (C, O-*C*=O), 143.5 (C), 141.5 (C), 138.8 (C), 138.2 (C), 136.6 (C), 130.1 (C), 129.5 (2CH), 128.7 (CH), 128.4 (2CH), 128.3 (2CH), 127.5 (2CH), 126.9 (CH), 125.6 (C), 124.7 (CH), 123.6 (CH), 114.8 (CH), 84.2 (C), 61.2 (CH_2), 52.3 (CH_2), 51.8 (C), 49.6 (CH), 44.4 (CH_2), 40.9 (CH_2), 40.9 (CH), 37.9 (CH), 31.0 (CH_2), 28.0 ($3CH_3$), 21.5 (CH_3), 13.4 (CH_3); HRMS (ESI) m/z: 707.23976 $[M + Na]^+$, calcd for $C_{38}H_{40}O_8N_2NaS$; Found 707.24184.

1'-(tert-butyl)6-ethyl(4R,5R,6R,7S)-5'-fluoro-2'-oxo-4-(2-oxoethyl)-7-phenyl-1-tosyl-1,2,3,4,6,7-hexahydrospiro[indole-5,3'-indoline]-1',6-dicarboxylate (4w):

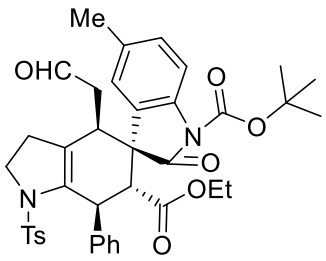


4w

Prepared by following general procedure **C** purified by column chromatography using EtOAc/hexane and isolated product **4w** in 85% yield as a pale yellow solid with M. P. 108 - 112 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IA column (hexane/EtOAc = 70:30, flow rate 0.5 mL/min, λ = 254 nm), t_R = 11.295 min (major), t_R = 12.189 min (minor), **$[\alpha]_D^{25}$ = +78.627 ($CHCl_3$, *c* = 1.35 g/100mL, $CHCl_3$ for 91% *ee*)**; IR (neat) ν_{max} 1724, 1481, 1249, 1149, 1022 and 586 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (1H, s), 7.87 – 7.83 (1H, m), 7.39 (2H, d, *J* = 8.4 Hz), 7.25 – 7.23 (3H, m), 7.16 – 7.14 (4H, m), 7.10 – 7.01 (2H, m), 4.79 –

4.75 (1H, m), 4.13 – 4.07 (1H, m), 3.83 – 3.74 (2H, m), 3.72 – 3.50 (2H, m), 3.33 (1H, d, *J* = 8.8 Hz), 3.08 (1H, d, *J*= 9.4 *Hz*), 2.58 – 2.49 (2H, m), 2.38 (4H, s), 1.58 (9H, s), 0.84 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT-135) δ 198.8 (C, H-*C*=O), 175.8 (C, N-*C*=O), 170.3 (C, O-*C*=O), 159.8 (C, d, *J* = 242 Hz), 148.7(C, O-*C*=O), 143.9 (C), 141.2 (C), 138.2 (C), 136.1 (C), 134.9 (C, d, *J* = 3 Hz), 131.9 (C, d, *J* = 9 Hz), 129.7 (2CH), 128.4 (2CH), 128.2 (2CH), 127.4 (2CH), 127.0 (CH), 125.8 (C), 116.1 (CH, d, *J* = 7 Hz), 115.2 (CH, d, *J* = 23 Hz), 111.4 (CH, d, *J* = 25 Hz), 84.4 (C), 61.3 (CH_2), 52.2 (CH), 51.9 (C), 49.6 (CH_2), 44.2 (CH_2), 40.9 (CH), 37.8 (CH), 30.9 (CH_2), 27.9 ($3CH_3$), 21.5 (CH_3), 13.4 (CH_3); HRMS (ESI) m/z: 725.23034 $[M + Na]^+$, calcd for $C_{38}H_{39}O_8N_2FNaS$; Found 725.23231.

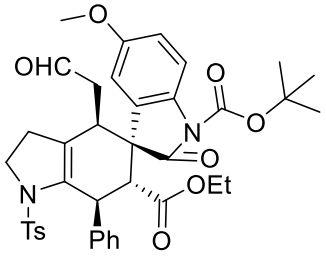
1'-(tert-butyl)6-ethyl(4R,5R,6R,7S)-5'-methyl-2'-oxo-4-(2-oxoethyl)-7-phenyl-1-tosyl-1,2,3,4,6,7-hexahydrospiro[indole-5,3'-indoline]-1',6-dicarboxylate (4x):



4x

Prepared by following general procedure **C** purified by column chromatography using EtOAc/hexane and isolated product **4x** in 86% yield as a pale yellow solid with M. P. 90 - 93 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IA column (hexane/EtOAc = 85:15, flow rate 0.5 mL/min, λ = 254 nm), t_R = 28.811 min (major), t_R = 31.719 min (minor), **$[\alpha]_D^{25}$ = +47.679 ($CHCl_3$, *c* = 1.36 g/100mL, $CHCl_3$ for 93% *ee*)**; IR (neat) ν_{max} 1724, 1489, 1249, 1149, 1022 and 586 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (1H, s), 7.72 (1H, d, *J* = 8.4 Hz), 7.43 (1H, s), 7.23 – 7.13 (8H, m), 7.03 (2H, d, *J* = 8.4 Hz), 4.82 – 4.79 (1H, m), 4.13 – 4.07 (1H, m), 3.79 – 3.71 (2H, m), 3.57 (1H, dd, *J* = 9.2, 9.2 Hz), 3.40 (1H, q, *J*= 9.6 Hz), 3.32 (1H, q, *J*= 9.6 Hz), 3.13 (1H, d, *J*= 8.4 Hz), 2.73 – 2.63 (1H, m), 2.53 (1H, dd, *J* = 2.8, 2.8 Hz), 2.39 (3H, s), 2.33 (4H, s), 1.59 (9H, s), 0.83 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT-135) δ 198.9 (C, H-*C*=O), 176.3 (C, N-*C*=O), 170.4 (C, O-*C*=O), 148.8 (C, O-*C*=O), 143.5 (C), 141.1 (C), 138.7 (C), 136.6 (C), 136.4 (C), 134.6 (C), 130.0 (C), 129.3 (2CH), 129.2 (CH), 128.5 (2CH), 128.3 (2CH), 127.4 (2CH), 126.9 (CH), 126.8 (C), 124.7 (CH), 114.5 (CH), 84.0 (C), 61.0 (CH_2), 52.1 (CH), 51.8 (C), 49.5 (CH_2), 44.3 (CH_2), 41.5 (CH), 38.1 (CH), 31.5 (CH_2), 28.0 ($3CH_3$), 21.4 (CH), 21.3 (CH_3), 13.4 (CH_3); HRMS (ESI) m/z: 721.25541 $[M + Na]^+$, calcd for $C_{39}H_{42}O_8N_2NaS$; Found 721.25805.

1'-(tert-butyl)6-ethyl(4R,5R,6R,7S)-5'-methoxy-2'-oxo-4-(2-oxoethyl)-7-phenyl-1-tosyl-1,2,3,4,6,7-hexahydrospiro[indole-5,3'-indoline]-1',6-dicarboxylate (4y):

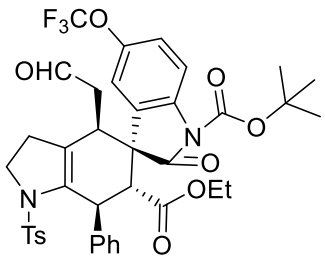


4y

Prepared by following general procedure **C** purified by column chromatography using EtOAc/hexane and isolated product **4y** in 95% yield as a pale yellow solid with M. P. 88 - 90 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IA column (hexane/EtOAc = 80:20, flow rate 0.5 mL/min, λ = 254 nm), t_R = 19.207 min (major), t_R = 46.590 min (minor), **$[\alpha]_D^{25}$ = +56.056 ($CHCl_3$, *c* = 1.58 g/100mL, $CHCl_3$ for 94% *ee*)**; IR (neat) ν_{max} 1724, 1489, 1276, 1149, 1022 and 586 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (1H, s), 7.77 (1H, d, *J* = 8.8 Hz), 7.26 – 7.24 (3H, m), 7.20 – 7.17 (3H, m), 7.10 – 7.08 (2H, m),

7.03 – 7.01 (2H, m), 6.90 (1H, dd, *J* = 2.4, 2.8 Hz), 4.88 – 4.84 (1H, m), 4.10 – 4.04 (1H, m), 3.90 (3H, s), 3.81 – 3.73 (2H, m), 3.59 (1H, dd, *J* = 9.2, 9.2 Hz), 3.35 – 3.32 (2H, m), 3.15 (1H, d, *J*= 9.2 Hz), 2.74 – 2.64 (1H, m), 2.53 (1H, dd, *J* = 2.8, 2.4 Hz), 2.33 (4H, s), 1.59 (9H, s), 0.84 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT-135) δ 198.9 (C, H-*C*=O), 176.2 (C, N-*C*=O), 170.3 (C, O-*C*=O), 157.2 (C), 148.8 (C, O-*C*=O), 143.5 (C), 140.9 (C), 138.7 (C), 136.5 (C), 132.0 (C), 131.2 (C), 129.3 (2CH), 128.7 (2CH), 128.4 (2CH), 127.3 (2CH), 126.9 (C), 115.1 (CH), 108.7 (CH), 84.0 (C), 61.1 (CH_2), 56.3 (CH), 52.1 (C), 52.0 (CH), 49.6 (CH_2), 44.4 (CH_2), 41.7 (CH), 38.1 (CH), 31.5 (CH_2), 28.0 ($3CH_3$), 21.5 (CH_3), 13.5 (CH_3); HRMS (ESI) m/z: 737.25032 $[M + Na]^+$, calcd for $C_{39}H_{42}O_9N_2NaS$; Found 737.25124.

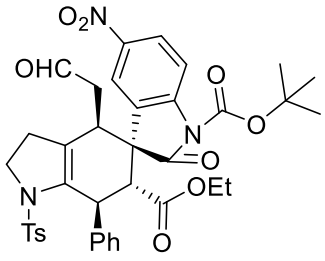
1'-(tert-butyl) 6-ethyl (4R,5R,6R,7S)-2'-oxo-4-(2-oxoethyl)-7-phenyl-1-tosyl-5'-(trifluoromethoxy)-1,2,3,4,6,7-hexahydrospiro[indole-5,3'-indoline]-1',6-dicarboxylate (4z):



4z

Prepared by following general procedure **C** purified by column chromatography using EtOAc/hexane and isolated product **4z** in 68% yield as a pale yellow solid with M. P. 89 - 92 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IA column (hexane/EtOAc = 80:20, flow rate 0.5 mL/min, λ = 254 nm), t_R = 14.052 min (major), t_R = 15.266 min (minor), **$[\alpha]_D^{25}$ = +74.492 ($CHCl_3$, *c* = 1.18 g/100mL, $CHCl_3$ for 92% *ee*)**; IR (neat) ν_{max} 1728, 1477, 1246, 1149, 1022 and 586 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.72 (1H, s), 7.92 (1H, d, *J* = 8.8 Hz), 7.38 (1H, br s), 7.24 – 7.22 (6H, m), 7.15 – 7.13 (2H, m), 7.06 (2H, d, *J* = 8 Hz), 4.80 – 4.78 (1H, m), 4.13 – 4.07 (1H, m), 3.82 – 3.73 (2H, m), 3.56 – 3.47 (2H, m), 3.36 (1H, d, *J* = 9.2 Hz), 3.11 (1H, d, *J*= 8.8 Hz), 2.62 – 2.50 (2H, m), 2.41 – 2.38 (1H, m), 2.34 (3H, s), 1.59 (9H, s), 0.84 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT-135) δ 198.8 (C, H-*C*=O), 175.6 (C, N-*C*=O), 170.3 (C, O-*C*=O), 148.6 (C, O-*C*=O), 145.9(C), 143.6 (C), 141.0 (C), 138.7 (C), 137.6 (C), 136.3 (C), 131.9 (C), 129.4 (CH), 128.5 (CH), 128.3 (CH), 127.4 (CH), 127.0 (CH), 125.3 (C), 120.5 (C, O-*C*F_3, *J* = 256 Hz), 115.8 (CH), 84.7 (C), 61.3 (CH_2), 52.2 (CH), 52.0 (C), 49.4 (CH_2), 44.2 (CH_2), 41.0 (CH), 37.8 (CH), 31.2 (CH_2), 27.9 ($3CH_3$), 21.5 (CH_3), 13.4 (CH_3); HRMS (ESI) m/z: 791.22206 $[M + Na]^+$, calcd for $C_{39}H_{39}O_9N_2F_3NaS$; Found 791.22483.

1'-(tert-butyl) 6-ethyl (4R,5R,6R,7S)-5'-nitro-2'-oxo-4-(2-oxoethyl)-7-phenyl-1-tosyl-1,2,3,4,6,7-hexahydrospiro[indole-5,3'-indoline]-1',6-dicarboxylate (4a'):

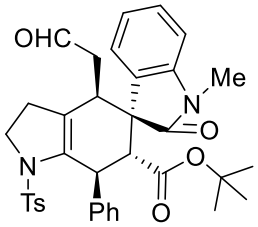


4a'

Prepared by following general procedure **C** purified by column chromatography using EtOAc/hexane and isolated product **4a'** in 89% yield as a pale yellow solid with M. P. 105 - 108 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IA column (hexane/EtOAc = 80:20, flow rate 0.5 mL/min, λ = 254 nm), t_R = 25.109 min (major), t_R = 32.155 min (minor), **$[\alpha]_D^{25}$ = +62.049 ($CHCl_3$, *c* = 1.47 g/100mL, $CHCl_3$ for 95% *ee*)**; IR (neat) ν_{max} 1724, 1523, 1342, 1149, 1022 and 586 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (1H, s), 8.48 (1H, d, *J* = 2.4 Hz), 8.34 – 8.31 (1H, m), 8.08 (1H, d, *J* = 8.8 Hz), 7.27 – 7.25 (3H, m), 7.21 – 7.17 (4H, m),

7.05 8.48 (2H, d, *J* = 8 Hz), 4.80 – 4.77 (1H, m), 4.11 – 4.05 (1H, m), 3.80 – 3.75 (2H, m), 3.56 (1H, dd, *J* = 9.6, 9.6 Hz), 3.44 – 3.36 (2H, m), 3.13 (1H, d, *J*= 9.2 Hz), 2.73 – 2.60 (2H, m), 2.34 (4H, s), 1.61 (9H, s), 0.84 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT-135) δ 198.7 (C, H-*C*=O), 175.6 (C, N-*C*=O), 170.5 (C, O-*C*=O), 148.2 (C, O-*C*=O), 144.9 (C), 144.3 (C), 143.5 (C), 140.5 (C), 139.3 (C), 136.5 (C), 131.7 (C), 129.4 (2CH), 128.7 (2CH), 128.4 (2CH), 127.4 (2CH), 127.2 (CH), 125.9 (C), 125.1 (CH), 119.3 (CH), 114.9 (CH), 85.4 (C), 61.3 (CH_2), 50.1 (CH), 51.6 (C), 49.6 (CH_2), 44.1 (CH_2), 42.1 (CH), 37.8 (CH), 31.4 (CH_2), 27.9 ($3CH_3$), 21.5 (CH_3), 13.5 (CH_3); HRMS (ESI) m/z: 752.22672 $[M + Na]^+$, calcd for $C_{38}H_{39}O_{10}N_3NaS$; Found 752.22672.

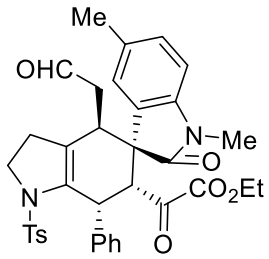
tert-butyl (4R,5R,6R,7S)-1'-methyl-2'-oxo-4-(2-oxoethyl)-7-phenyl-1-tosyl-1,2,3,4,6,7-hexahydrospiro[indole-5,3'-indoline]-6-carboxylate (4b'):



4b'

Prepared by following general procedure **C** purified by column chromatography using EtOAc/hexane and isolated product **4b'** in 66% yield as a pale yellow solid with M. P. 96 - 101 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IA column (hexane/EtOAc = 80:20, flow rate 0.5 mL/min, λ = 254 nm), t_R = 39.187 min (minor), t_R = 41.753 min (major), **$[\alpha]_D^{25}$ = +85.117 ($CHCl_3$, *c* = 0.94 g/100mL, $CHCl_3$ for 98% *ee*)**; IR (neat) ν_{max} 1728, 1492, 1350, 1153, 1022 and 586 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.73 (1H, s), 7.33 – 7.27 (3H, m), 7.23 – 7.22 (4H, m), 7.15 – 7.11 (4H, m), 6.96 (1H, t, *J* = 7.2 Hz), 6.84 (1H, d, *J* = 8 Hz), 4.75 – 4.71 (1H, m), 4.19 – 4.13 (1H, m), 3.67 – 3.54 (2H, m), 3.14 (1H, d, *J* = 9.6 Hz), 3.11 (3H, s), 3.02 (1H, d, *J*= 9.2 Hz), 2.64 – 2.54 (1H, m), 2.43 (1H, dd, *J* = 2.4, 2.4 Hz), 2.39 (4H, s), 1.01 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT-135) δ 199.3 (C, H-*C*=O), 176.8 (C, N-*C*=O), 169.3 (C, O-*C*=O), 143.4 (C), 142.7 (C), 141.3 (C), 138.0 (C), 136.7 (C), 131.4 (C), 129.5 (2CH), 128.4 (2CH), 128.3 (2CH), 127.5 (2CH), 126.5 (C), 124.1 (CH), 122.9 (CH), 81.1 (C), 52.6 (CH), 51.3 (C), 49.6 (CH_2), 43.9 (CH_2), 41.5 (CH), 31.0 (CH_2), 27.3 (CH), 21.5 (CH_3); HRMS (ESI) m/z: 649.23428 $[M + Na]^+$, calcd for $C_{36}H_{38}O_6N_2NaS$; Found 649.23674.

ethyl 2-((4R,5R,6R,7R)-1',5'-dimethyl-2'-oxo-4-(2-oxoethyl)-7-phenyl-1-tosyl-1,2,3,4,6,7-hexahydrospiro[indole-5,3'-indolin]-6-yl)-2-oxoacetate (4'a):

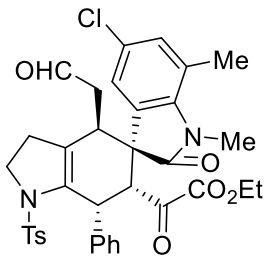


4'a

Prepared by following general procedure **D** purified by column chromatography using EtOAc/hexane and isolated product **4'a** in 63% yield as a yellow sesemi-solidThe enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IA column (hexane/EtOAc = 70:30, flow rate 1 mL/min, λ = 254 nm), t_R = 9.162 min (major), t_R = 18.679 min (minor), **$[\alpha]_D^{25}$ = -160.440 ($CHCl_3$, *c* = 0.186 g/100mL, $CHCl_3$ for 99% *ee*)**; IR (neat) ν_{max} 2931, 1705, 1496, 1350, 1157 and 817 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (1H, s), 8.10 (2H, d, *J* = 8 Hz), 7.32 (2H, d, *J* = 8 Hz), 7.22 (2H, d, *J* = 7.6 Hz), 7.16 – 7.05 (4H, m), 6.72 (1H, d, *J* = 8 Hz), 6.64 (1H, s), 5.16 (1H, br s), 4.38 (1H, d, *J = 7.2 Hz*), 4.06 (1H, br s), 3.76 – 3.68 (3H, m), 3.66 - 3.60 (1H, m), 3.29 (3H, s), 2.43 (4H, s), 2.19 (3H, m), 1.97 – 1.93 (1H, m), 1.83 – 1.77 (1H, m), 1.00 (3H, t, *J* = 7.2 Hz); ^{13}C NMR

(100 MHz, $CDCl_3$, DEPT-135) δ 199.9 (C, H-*C*=O), 194.6 (C,*C*=O), 175.1 (C, N-*C*=O), 159.2 (C, O-*C*=O), 143.6 (C), 141.5 (C), 136.1 (C), 135.8 (C), 134.1 (C), 132.6 (C), 131.8 (C), 130.5 (CH), 129.9 (2CH), 129.4 (2CH), 128.8 (2CH), 128.3 (2CH), 127.9 (CH), 125.1 (CH), 108.3 (CH), 62.3 (CH_2), 51.9 (CH), 49.7 (CH), 49.6 (CH_2), 42.0 (CH_2), 41.4 (CH), 34.8 (CH), 30.9 (CH_2), 26.4 (CH_3), 21.6 (CH_3), 21.2 (CH_3), 13.7 (CH_3); HRMS (ESI) m/z: 663.21354 $[M + Na]^+$, calcd for $C_{36}H_{36}O_7N_2NaS$; Found 663.21302.

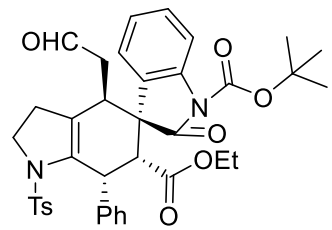
ethyl 2-((4R,5R,6R,7R)-5'-chloro-1',7'-dimethyl-2'-oxo-4-(2-oxoethyl)-7-phenyl-1-tosyl-1,2,3,4,6,7-hexahydrospiro[indole-5,3'-indolin]-6-yl)-2-oxoacetate (4'l):



4'l

Prepared by following general procedure **D** purified by column chromatography using EtOAc/hexane and isolated product **4'l** in 83% yield as a yellow ssemi-solid The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IA column (hexane/EtOAc = 70:30, flow rate 0.5 mL/min, λ = 254 nm), t_R = 18.913 min (major), t_R = 49.215 min (minor), **$[\alpha]_D^{25}$ = -129.187 ($CHCl_3$, *c* = 0.105 g/100mL, $CHCl_3$ for 99% *ee*)**; IR (neat) ν_{max} 2924, 1712, 1597, 1458, 1342 and 1157 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.21 (1H, t, *J* = 2 Hz), 8.08 (2H, d, *J* = 8.4 Hz), 7.32 (2H, d, *J* = 8 Hz), 7.22 (2H, d, *J* = 7.6 Hz), 7.19 – 7.09 (2H, m), 7.08 - 7.07 (1H, m), 6.99 (1H, d, *J* = 1.6 Hz), 6.65 (1H, d, *J* = 2 Hz), 5.1 (1H, br s), 4.35 (1H, d, *J* = 6.8 Hz), 3.99 (1H, br s), 3.80 - 3.72 (3H, m), 3.64 – 3.58 (3H, m), 2.55 (3H, s), 2.43 (4H, s), 2.15 – 2.09 (1H, m), 1.99 – 1.94 (1H, m), 1.85 – 1.79 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT-135) δ 199.7 (C, H-*C*=O), 194.4 (C,*C*=O), 175.4 (C, N-*C*=O), 159.3 (C, O-*C*=O), 143.7 (C), 140.4 (C), 135.8 (C), 134.0 (C), 132.9 (CH), 131.5 (C), 130.5 (2CH), 129.3 (2CH), 128.8 (C), 128.8 (2CH), 128.3 (C), 127.8 (C), 126.9 (CH), 122.4 (CH), 121.7 (C), 62.5 (CH_2), 51.5 (C), 49.6 (CH), 49.6 (CH_2), 41.9 (CH_2), 41.4 (CH), 34.8 (CH), 30.9 (CH_2), 29.8 (CH_3), 21.6 (CH_3), 19.0 (CH_3), 13.7 (CH_3); HRMS (ESI) m/z: 697.17457 $[M + Na]^+$, calcd for $C_{36}H_{35}O_7N_2ClNaS$; Found 697.17376.

1'-(tert-butyl)6-ethyl(4R,5R,6R,7R)-2'-oxo-4-(2-oxoethyl)-7-phenyl-1-tosyl-1,2,3,4,6,7-hexahydrospiro[indole-5,3'-indoline]-1',6-dicarboxylate (4'v):

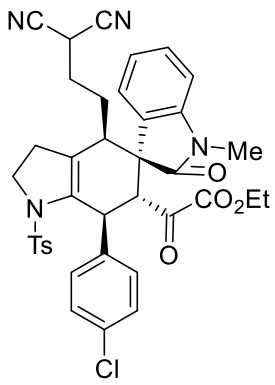


4'v

Prepared by following general procedure **D** purified by column chromatography using EtOAc/hexane and isolated product **4'v** in 84% yield as a yellow ssemi-solid The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak IA column (hexane/EtOAc = 80:20, flow rate 0.5 mL/min, λ = 254 nm), t_R = 20.378 min (major), t_R = 47.689 min (minor), **$[\alpha]_D^{25}$ = -21.835 ($CHCl_3$, *c* = 0.609 g/100mL, $CHCl_3$ for 99% *ee*)**; IR (neat) ν_{max} 2924, 1724, 1346, 1249, 1149 and 678 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.28 (1H, s), 8.08 (2H, d, *J* = 8 Hz), 7.84 (1H, d, *J* = 8 Hz), 7.31 (4H, d, *J* = 8 Hz), 7.20 – 7.18 (5H, m), 7.09 – 7.06 (1H, m), 4.93 (1H, br s), 4.11 – 4.09 (1H, m), 3.81 – 3.74 (2H, m), 3.61 – 3.56 (1H, m), 3.47 – 3.41 (1H, m), 3.10 (1H, d, *J*= 6.8 *Hz*), 2.44 (3H, s), 2.38 (1H, d, *J* = 9.6 Hz), 2.21 – 2.14 (1H, m), 1.96 – 1.87 (1H, m), 1.83 (1H, m), 1.73 (9H, s), 0.64 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT-135) δ 199.4 (C, H-*C*=O), 173.5 (C, N-

C=O), 169.9 (C, O-*C*=O), 149.0 (C, O-*C*=O), 143.6 (C), 139.8 (C), 138.1 (C), 135.7 (C), 134.1 (C), 130.6 (C), 129.7 (CH), 129.3 (2CH), 128.8 (2CH), 127.9 (2CH), 127.5 (CH), 127.5 (CH), 126.7 (CH), 124.8 (CH), 123.8 (2CH), 115.0 (CH), 84.9 (C), 60.3 (CH_2), 53.7 (CH), 51.9 (C), 49.6 (CH_2), 42.0 (CH_2), 40.9 (CH), 34.7 (CH), 30.8 (CH_2), 28.2 ($3CH_3$), 21.7 (CH_3), 13.4 (CH_3); HRMS (ESI) m/z: 707.23976 [M + Na]$^+$, calcd for $C_{38}H_{40}O_8N_2NaS$; Found 707.23977.

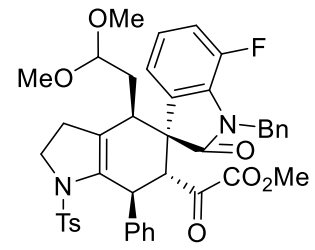
ethyl 2-((4R,5R,6R,7S)-7-(4-chlorophenyl)-4-(3,3-dicyanopropyl)-1'-methyl-2'-oxo-1-tosyl-1,2,3,4,6,7-hexahydrospiro[indole-5,3'-indolin]-6-yl)-2-oxoacetate (5t):



5t

Prepared by following general procedure **E** purified by column chromatography using EtOAc/hexane and isolated product **5t** in 70% yield as a white solid with M. P. 102 - 105 °C. **$[\alpha]_D^{25}$ = +234.773 ($CHCl_3$, *c* = 0.37 g/100mL, $CHCl_3$)**; IR (neat) ν_{max} 2924, 2360, 1701, 1612 1492, 1157, and 1091 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (1H, d, *J* = 7.6 Hz), 7.39 (1H, t, *J* = 7.6 Hz), 7.19 (7H, m), 6.97 (2H, d, *J* = 8.4 Hz), 6.89 (1H, d, *J* = 8 Hz), 4.52 (1H, d, *J* = 10.4 Hz), 4.32 – 4.23 (2H, m) 4.0 – 3.85 (3H, m), 3.60 (1H, q, *J* = 10 Hz), 3.15 (3H, s), 2.75 – 2.68 (1H, m), 2.54 (1H, dd, *J* = 9.2, 9.2 Hz), 2.45 – 2.39 (4H, m), 2.34 – 2.25 (2H, m), 2.05 – 1.94 (2H,m), 1.14 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT-135) δ 193.9 (C, *C*=O), 175.7 (C, *C*=O), 160.8 (C, N-*C*=O), 143.7 (C), 141.1 (C), 138.2 (C), 137.2 (C), 136.8 (C), 133.4 (C), 130.1 (2CH), 130.0 (C) 129.4 (2CH), 129.1 (CH), 128.7 (2CH), 127.1 (C), 126.8 (2CH), 124.3 (CH), 124.1 (CH), 112.5 (CN), 112.5 (CN), 108.8 (CH), 62.6 (CH_2), 52.7 (CH), 51.9 (C), 49.9 (CH_2), 43.4 (CH), 42.2 (CH), 31.5 (CH_2), 30.3 (CH_2), 27.5 (CH_2), 26.5 (CH), 22.7 (CH_3), 21.6 (CH_3), 13.7 (CH_3); HRMS (ESI) m/z: 733.18580 [M + Na]$^+$, calcd for $C_{38}H_{35}O_6N_4ClNaS$; Found 733.18364.

methyl 2-((4R,5R,6R,7S)-1'-benzyl-4-(2,2-dimethoxyethyl)-7'-fluoro-2'-oxo-7-phenyl-1-tosyl-1,2,3,4,6,7-hexahydrospiro[indole-5,3'-indolin]-6-yl)-2-oxoacetate (6s):

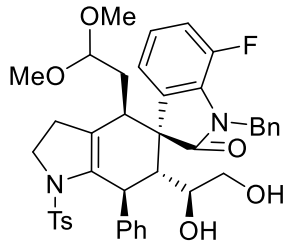


6s

Prepared by following general procedure **F** purified by column chromatography using EtOAc/hexane and isolated product **6s** in 87% yield as a white solid with M. P. 108 - 111 °C. **$[\alpha]_D^{25}$ = +209.266 ($CHCl_3$, *c* = 0.52 g/100mL, $CHCl_3$)**; IR (neat) ν_{max} 2924, 1735, 1705, 1450, 1157, and 1080 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (1H, dd, *J* = 2.4, 2.4 Hz), 7.33 – 7.27 (3H, m), 7.25 – 7.19 (4H, m), 6.95 (1H, ddd, *J* = 2, 2, 2 Hz), 6.66 (1H, dd, *J* = 4.4, 4.4 Hz), 5.01 (1H, d, *J* = 16 Hz), 4.66 (1H, d, *J* = 16 Hz), 4.50 (1H, d, *J* = 10.4 Hz), 4.44 (1H, d, *J* = 10.8 Hz), 4.16 – 4.09 (2H, m), 3.48 (1H, q, *J* = 11.2 Hz), 3.41 (3H, s), 3.28 (3H, s), 3.18 (3H, s), 3.00 (1H, dt, *J* = 4.4,, 14.8 Hz) 2.67 – 2.49 (2H, m), 2.34 (4H, s), 1.81 – 1.77 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT-135) δ 195.1 (C, *C*=O), 176.4 (C, *C*=O), 160.8 (C, *C*=O),159.5 (C-F, d, *J* = 240 Hz), 143.5 (C), 139.0 (C), 137.8 (C, d, *J* = 2Hz), 136.6 (C), 136.5 (C), 135.4 (C), 132.7 (C, d, *J* = 8 Hz), 130.7 (C), 129.4 (2CH) 128.8 (2CH), 128.7 (CH), 128.5 (2CH), 127.7 (CH), 127.4 (CH), 127.3 (2CH), 127.1 (2CH), 114.7 (C, d, *J* = 23 Hz), 113.0 (C, d, *J* = 26 Hz), 109.7 (C, d, *J* = 8 Hz), 104.2 (CH), 54.3 (CH_3), 54.1 (CH_3), 52.7 (CH_3), 52.5 (CH), 52.4 (C), 50.0 (CH_2),

44.0 (CH_2), 43.4 (CH), 39.7 (CH), 33.7 (CH_2), 31.6 (CH_2), 21.5 (CH_3),; HRMS (ESI) m/z: 775.24599 [M + Na]$^+$, calcd for $C_{42}H_{41}O_8N_2FNaS$; Found 775.24691.

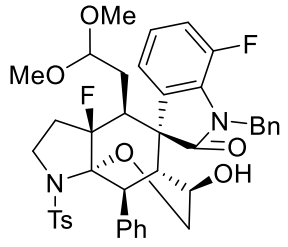
(4R,5R,6R,7S)-1'-benzyl-6-((S)-1,2-dihydroxyethyl)-4-(2,2-dimethoxyethyl)-7'-fluoro-7-phenyl-1-tosyl-1,2,3,4,6,7-hexahydrospiro[indole-5,3'-indolin]-2'-one (7s):



7s

Prepared by following general procedure **G** purified by column chromatography using EtOAc/hexane and isolated product **7s** in 83% yield as a white solid with M. P. 87 - 90 °C. **[α]$_D^{25}$ = +167.415 ($CHCl_3$, *c* = 0.18 g/100mL, $CHCl_3$)**; IR (neat) ν_{max} 3398, 2924, 1701, 1450, 1153, and 1080 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.26 (13H, m), 7.14 (2H, d, *J* = 8 Hz), 6.93 (1H, ddd, *J* = 2.4, 2.4, 2.4 Hz), 6.70 (1H, dd, *J* = 4.0, 4.0 Hz), 5.15 (1H, d, *J* = 15.6 Hz), 4.68 (1H, d, *J* = 15.6 Hz), 4.30 (1H, d, *J* = 6.8 Hz), 4.09 (1H, q, *J* = 3.6 Hz), 3.91 (1H, t, *J* = 8.8 Hz), 3.59 (3H, bs), 3.30 (3H, s), 3.27 – 3.18 (5H, m), 3.11 – 3.02 (2H, m), 2.89 (1H, t, *J* = 7.2 Hz), 2.44 – 2.36 (5H, m), 2.11 (1H, t, *J* = 4.4 Hz), 1.78 – 1.69 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT-135) δ 179.6 (C, *C*=O), 159.0 (C-F, d, *J* = 239 Hz), 143.6 (C), 142.1 (C), 138.2 (C), 136.7 (C), 136.0 (C), 134.9 (C, d, *J* = 8 Hz), 130.2 (C), 129.5 (2CH) 129.1 (2CH), 128.8 (2CH), 128.8 (2CH), 127.7 (CH), 127.5 (2CH), 127.4 (2CH), 127.2 (CH), 114.1 (C, d, *J* = 23 Hz), 112.9 (C, d, *J* = 25 Hz), 109.5 (C, d, *J* = 8 Hz), 104.6 (CH), 74.8 (CH), 65.1 (CH_2), 54.3 (CH_3), 54.2 (CH_3), 52.4 (C), 50.6 (CH_2), 46.2 (CH), 44.5 (CH), 44.3 (CH_2), 40.1 (CH), 34.7 (CH_2), 31.2 (CH_2), 21.5 (CH_3); HRMS (ESI) m/z: 749.26672 [M + Na]$^+$, calcd for $C_{41}H_{43}O_7N_2FNaS$; Found 749.26355.

(3S,3'R,4'R,6'S,6a'S,9a'S,10'S)-1-benzyl-6'-(2,2-dimethoxyethyl)-6a',7-difluoro-3'-hydroxy-10'-phenyl-9'-tosyl-3',4',6a',7',8',9'-hexahydro-2'H,6'H-spiro[indoline-3,5'-[4,9a]methanooxocino[2,3-b]pyrrol]-2-one (8s):

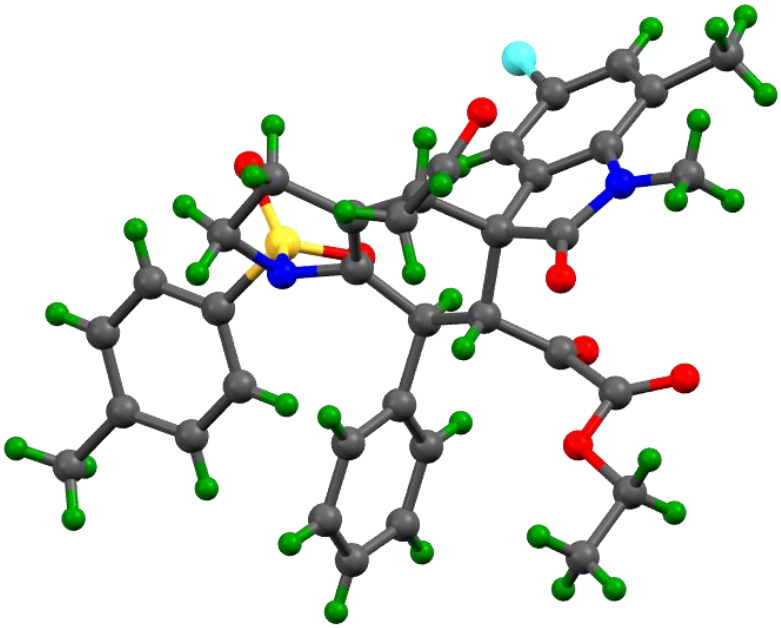


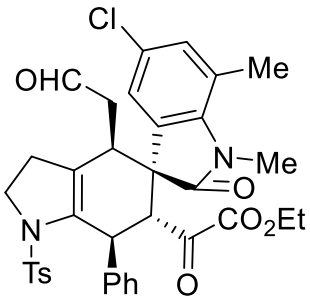
8s

Prepared by following general pr,procedure **H** purified by column chromatography using EtOAc/hexane and isolated product **8s** in 63% yield as a white solid with M. P. 144 - 147 °C. **[α]$_D^{25}$ = +18.857 ($CHCl_3$, *c* = 0.16 g/100mL, $CHCl_3$)**; IR (neat) ν_{max} 3448, 2924, 1720, 1492, 1157, and 671 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (2H, d, *J* = 8.4 Hz), 7.47 (2H, d, *J* = 7.2 Hz), 7.33 – 7.27 (3H, m), 7.24 – 7.10 (7H, m), 6.93 – 6.88 (2H, m), 6.62 (1H, dd, *J* = 2.4, 4.4, 4.4 Hz), 5.16 (1H, s), 4.80 (1H, d, *J* = 15.2 Hz), 4.59 (1H, t, *J* = 6.8 Hz), 4.33 – 4.24 (2H, m), 4.11 (1H, dd, *J* = 6.8, 6.8 Hz), 3.84 – 3.77 (2H, m), 3.64 (1H, sext, *J* = 6.8 Hz), 3.05 (3H, s), 2.97 (3H, s), 2.70 (1H, dt, *J* = 4.8, 4.8 Hz), 2.61 (1H, s), 2.43 (3H, s), 2.36 – 2.20 (2H, m), 1.94 – 1.87 (2H, m), 1.07 (1H, dt, *J* = 5.2, 5.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT-135) δ 175.1 (C, *C*=O), 158.0 (C-F, d, *J* = 239 Hz), 143.6 (C), 139.6 (C), 138.8 (C), 136.6 (C), 136.2 (C), 130.9 (C), 130.8 (C), 129.3 (2CH) 128.7 (2CH), 128.3 (CH), 128.2 (CH), 128.0 (2CH), 127.9 (2CH), 127.7 (CH), 126.9 (2CH), 125.1 (CH), 115.2 (C, d, *J* = 22 Hz), 114.4 (C, d, *J* = 24 Hz), 109.0 (C, d, *J* = 8 Hz), 102.8 (CH), 102.3 (C-F, d, *J* = 195 Hz), 96.5 (C, d, *J* = 23 Hz), 69.8 (CH), 66.3 (CH_2), 54.1 (C), 54.0 (CH_3), 52.4 (CH_3), 50.9 (CH), 46.0 (CH_2), 43.6 (CH_2), 39.0 (CH, d, J = 22Hz), 37.6 (CH), 32.4

(CH_2, d, J = 24 Hz),), 30.5 (CH_2, d, J = 5 Hz), 21.6 (CH_3); ^{19}F NMR (376MHz, $CDCl_3$) δ -121.25, -158.77; HRMS (ESI) m/z: 767.2573 $[M + Na]^+$, calcd for $C_{41}H_{42}O_7N_2F_2NaS$; Found 767.2542.

Single Crystal X-ray data for (+)-4l





(+)-4l

Table 1. Crystal data and structure refinement for **(+)-4l**

Identification code	shelx	
Empirical formula	C36 H35 Cl N2 O7 S	
Formula weight	675.17	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 14.5446(12) Å	α= 90°.
	b = 7.9372(6) Å	β= 107.170(3)°.
	c = 15.4692(13) Å	γ = 90°.
Volume	1706.2(2) $Å^3$	
Z	2	
Density (calculated)	1.314 Mg/m^3	
Absorption coefficient	0.224 mm^{-1}	

F(000)	708
Crystal size	0.401 x 0.069 x 0.042 mm^3
Theta range for data collection	3.380 to 25.499°.
Index ranges	-17<=h<=17, -9<=k<=9, -18<=l<=18
Reflections collected	30192
Independent reflections	6329 [R(int) = 0.1250]
Completeness to theta = 25.242°	99.6 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9705 and 0.4388
Refinement method	Full-matrix least-squares on F^2
Data/restraints / parameters	6329 / 1 / 427
Goodness-of-fit on F^2	1.033
Final R indices [I>2sigma(I)]	R1 = 0.0542, wR2 = 0.1133
R indices (all data)	R1 = 0.0898, wR2 = 0.1314
Absolute structure parameter	0.06(6)
Extinction coefficient	n/a
Largest diff. peak and hole	0.162 and -0.257 e.$Å^{-3}$