catalysts

MDPI

Communication

Organocatalytic, Asymmetric [2+2+2] Annulation to Construct Six-Membered Spirocyclic Oxindoles with Six Continuous Stereogenic Centers

Zhi-Long Li [1], Chao Liu [2], Rui Tan [1,*], Zhi-Ping Tong [1,*] and Yan-Kai Liu [2,*]

[1] School of Life Science and Engineering, Southwest Jiaotong University, Chengdu 610031, China; zhi-long_li@outlook.com

[2] Key Laboratory of Marine Drugs, Chinese Ministry of Education, School of Medicine and Pharmacy, Ocean University of China, Qingdao 266003, China; 17864275065@163.com

* Correspondence: tanrui@home.swjtu.edu.cn (R.T.); jk_reminder@163.com (Z.-P.T.); liuyankai@ouc.edu.cn (Y.-K.L.); Tel.: +86-532-8203-1905 (Y.-K.L.)

Academic Editor: Aurelio G. Csákÿ
Received: 17 March 2016; Accepted: 15 April 2016; Published: 27 April 2016

Abstract: Lactols and cyclic hemiaminals were directly used in a one-pot organo/organo dual catalytic system induced [2+2+2] tandem reaction for the asymmetric construction of six-membered carbocycles. The enamine-based stereoselective Michael addition of lactols or cyclic hemiaminals to electron-deficient olefinic oxindole motifs provided chiral C4 components, which were further combined with triethylamine catalyzed Michael/Henry sequential reactions affording spirocyclic oxindole derivatives containing six continuous stereogenic centers with excellent enantioselectivities as a single diastereoisomer. All these desired products have versatile molecular complexity, which might have potential applications in synthetic organic chemistry and the pharmaceutical industry.

Keywords: asymmetric organocatalysis; tandem reaction; lactol; cyclic hemiaminal; [2+2+2] annulation; spirocyclic oxindole

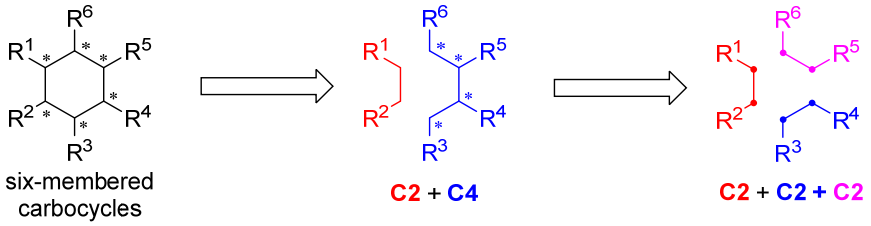
1. Introduction

One-pot organocatalytic multicomponent reaction, which could meet the demands of atom economy and efficiency, has proven to be a promising approach for the preparation of chiral organic molecules with multistereogenic centers [1–5]. Over the past few years, the combination of dual catalytic systems into asymmetric one-pot tandem procedures has been paid much attention due to the fact that this could provide effective access to valuable chiral complex structures from simple precursors via sequential processes. Compared with the costly organo/metal dual catalytic system-induced one-pot sequential processes [6–13], organo/organo catalysis is more experimentally simple and environmentally friendly which could support the development of green and sustainable chemistry [14–20].

Six-membered carbocycles can be found in many nature products and bioactive molecules [21,22]. As a result, great efforts have been devoted towards the development of practical methods for the production of these types of compounds with diverse substitution patterns [23–27]. However, concerning both the number of total stereoisomers and molecular complexity, it is challenging to stereoselectively install six continuous stereogenic centers on a six-membered ring, especially one containing spirocyclic oxindole structures which might have potential bioactivity [28–37]. Among the reported approaches, the organocatalyzed [2+2+2] tandem cycloaddition has emerged as a pivotal strategy to construct fully substituted six-membered carbocycles (Scheme 1) [38–40].

Very recently, we and others independently reported research on the application of lactols or cyclic hemiaminals as nucleophiles under enamine activation to produce chiral substituted lactones, lactams,

and other interesting heterocycles with excellent enantioselectivity and diastereoselectivity [41–46]. In an effort to expand our exploration on the application of lactols or cyclic hemiaminals, herein we would like to report an asymmetric [2+2+2] annulation under an organo/organo dual catalytic system to produce six-membered carbocycles with six continuous stereogenic centers including an all-carbon quaternary center and spirooxindole moiety in the product structure.



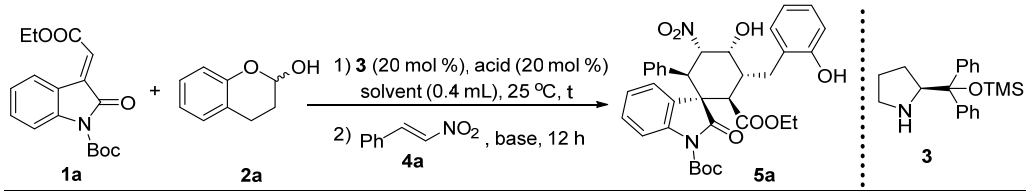
Scheme 1. [2+2+2] tandem reaction to synthesize six-membered carbocycles with six continuous stereogenic centers.

2. Results and Discussion

We first investigated the reaction of N-Boc-protected olefinic oxindole **1a** and lactol **2a** in the presence of commercially available chiral catalyst **3** and 4-NO_2PhCOOH in CH_3CN as the solvent at room temperature. After the enamine-based Michael addition step was completed, the β-nitrostyrene **4a** was then directly added to the crude reaction mixture and *N*,*N*-diisopropylethylamine (DIPEA) was used as the base catalyst to promote the sequential Michael/Henry cascade additions. To our gratification, this organo/organo dual catalytic system trigged [2+2+2] tandem reaction proceeded smoothly, leading to fully substituted spirocyclic six-membered carbocycles **5a** in 81% yield with high enantioselectivity as a single diastereoisomer (Table 1, entry 1). Similar results were attained with other acid additives (Table 1, entries 2–4). Interestingly, the reaction gave better stereocontrolled results when the less sterically hindered base, triethylamine (TEA), was used (Table 1, entry 5). Moreover, the inorganic base (K_2CO_3) could also catalyze the reaction and gave excellent enantioselectivity, albeit in lower yield (Table 1, entry 6). After screening a variety of solvents, EtOH with 5% H_2O was found to be the best solvent system (Table 1, entries 7–11). To have a more efficient process, the catalyst loading was decreased to 5 mol %. Notably, both the isolated yield and enantioselectivity of this elegant [2+2+2] cyclization reaction were maintained (Table 1, entry 12).

With the optimized conditions in hand (Table 1, entry 11), we next explored the substrate scope and limitations of this organo/organo dual catalytic system induced one-pot Michael/Michael/Henry tandem reaction. As shown in Scheme 2, various olefinic oxindole **1**, lactol **2**, and nitroolefin **4** were subjected to this asymmetric [2+2+2] annulation. Concerning the scope of nitroolefin **4**, good yields (71%–88%) and excellent enantioselectivities (93%–99%) were obtained irrespective of substituent positions and electronic properties changed on the aromatic ring (**5a**–**i**). Heteroaromatic groups, such as furan, thiophene, and indole, could also be used as the substituent of the nitroolefin **4** leading to the desired products with excellent enantioselectivity (**5j**–**l**). In the case of olefinic oxindole **1**, high reactivity had been observed regardless of the substituents on the aromatic groups (**5m**–**r**). Furthermore, various substituted lactol **2** proved to be suitable substrates, the expected spirocyclic products **5s**–**v** were obtained in high yields and excellent stereoselectivities. Additionally, the ester moiety has no effect on the reaction process (**5w**). It should be noted that not only lactol but also cyclic hemiaminal could be used and thus lead to the formation of **5x** with a Tos-protected amino group in the structure.

Table 1. Screening studies for the [2+2+2] annulation to synthesize six-membered carbocycles [a].



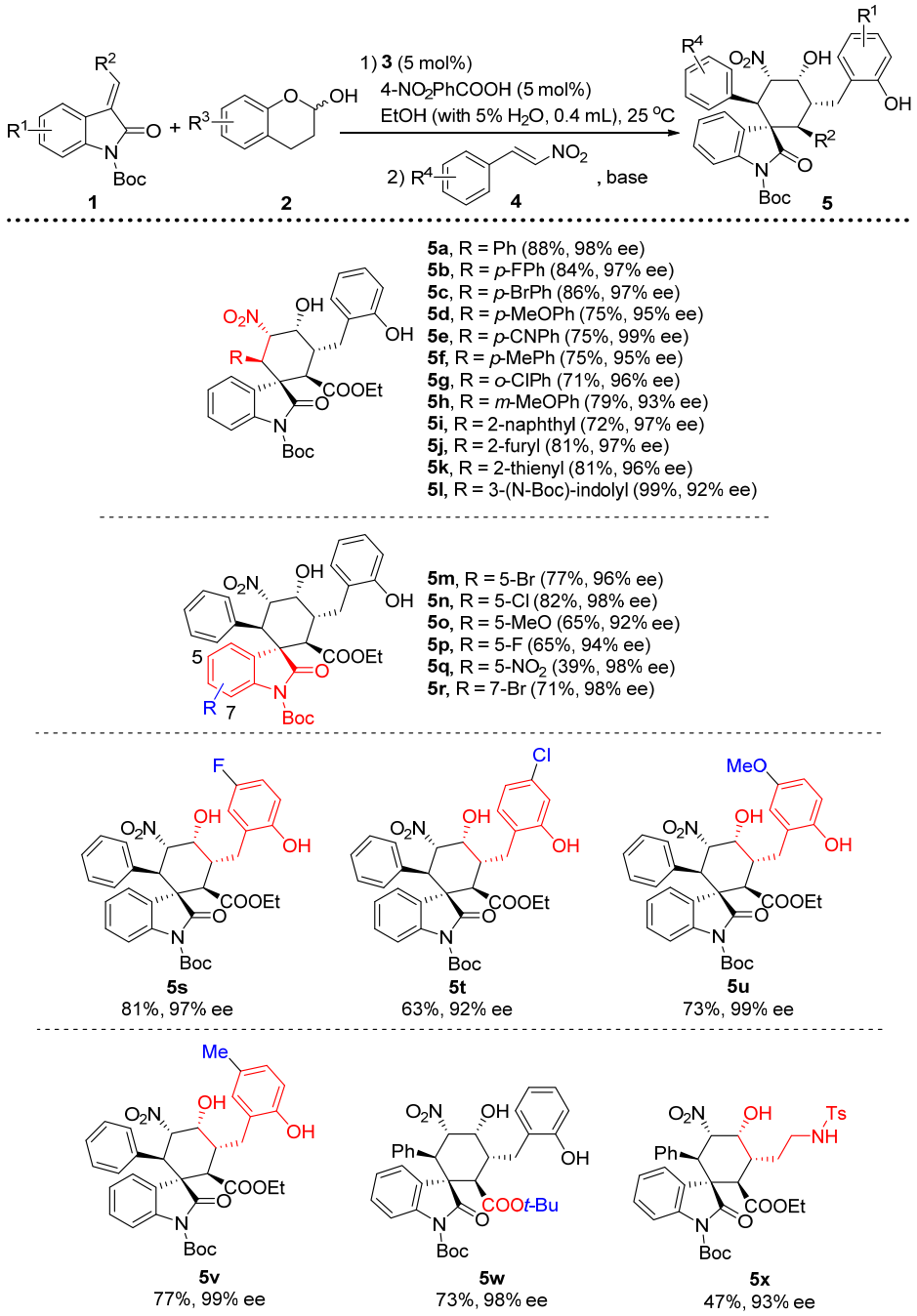
Entry	Solvent	Acid	Base	t [h]	Yield (%) [b]	Ee (%) [c]
1	CH_3CN	4-NO_2PhCOOH	DIPEA	12	81	93
2	CH_3CN	PhCOOH	DIPEA	16	76	93
3	CH_3CN	4-MeOPhCOOH	DIPEA	16	79	93
4	CH_3CN	2-FPhCOOH	DIPEA	12	81	93
5	CH_3CN	4-NO_2PhCOOH	TEA	12	84	97
6	CH_3CN	4-NO_2PhCOOH	K_2CO_3	6	77	97
7	Toluene	4-NO_2PhCOOH	TEA	24	88	93
8	CH_2Cl_2	4-NO_2PhCOOH	TEA	24	75	97
9	THF	4-NO_2PhCOOH	TEA	36	75	97
10	EtOH	4-NO_2PhCOOH	TEA	2	75	95
11 [d]	EtOH	4-NO_2PhCOOH	TEA	1	82	97
12 [e]	EtOH	4-NO_2PhCOOH	TEA	3	88	98

Notes: [a] Unless noted otherwise, reactions were carried out with **1a** (0.1 mmol), **2a** (0.12 mmol), **3** (0.02 mmol) and acid (0.02 mmol) in 0.4 mL of solvent at room temperature. After full conversion of the first step, **4a** (0.12 mmol) and base (0.04 mmol) were added to react for another 12 h. [b] Yield of isolated **5a**. [c] Enantiomeric excess (ee) was determined by HPLC analysis on a chiral stationary phase. dr > 20:1. [d] 5% H_2O was added. [e] 5 mol% **3** was used. THF = tetrahydrofuran; TMS = trimethylsilyl.

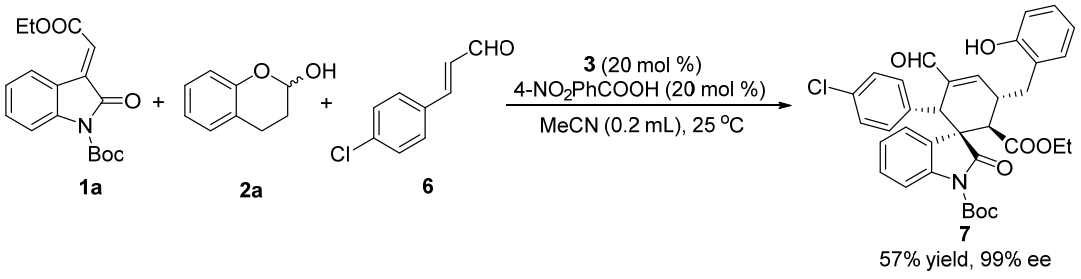
Moreover, the one-pot [2+2+2] cyclization between olefinic oxindole **1a**, lactol **2a** and cinnamaldehyde **6** was also investigated under slightly modified conditions. It was pleasing that the cascade reaction proceeded well and provided the desired product **7** in good yield with excellent stereoselectivity (Scheme 3) [38].

Unfortunately, we finally could not obtain any single crystal of product **5** or **7,** which is suitable for X-ray crystallographic analysis, while we obtained a single crystal of racemate **5g** which could provide the relative configuration of all the substituents on the ring system. Accordingly, as shown in Figure 1, we could propose the absolute configuration of both adduct **5g** and its enantiomer **5g′** [47].

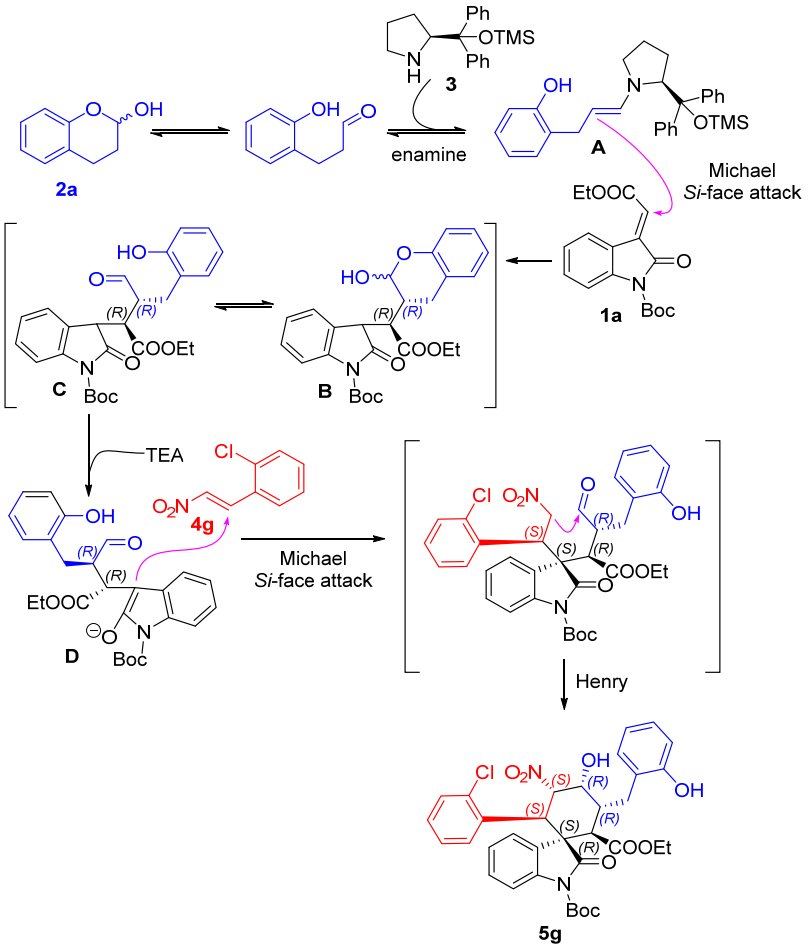
The detailed process of this one-pot organo/organo dual catalytic system-induced [2+2+2] annulation is depicted in Scheme 4 to rationalize the proposed stereochemistry of the products **5g**. According to our previously developed enamine-based asymmetric Michael reaction of lactol **2a**, the (*S*)-diphenylprolinol TMS ether **3** showed the same catalytic behavior, as in the asymmetric Michael reaction of aliphatic aldehydes, for the stereoselectivity control of the reaction process [41]. Thus, in the first step of this one-pot process, reaction of **3** with the lactol **2a** affords the enamine **A**, which allows for *si*-face attack of the olefinic oxindole **1a**, leading to formation of lactol **B** with (*R*,*R*)-configured stereocenters. This should be consistent with the observations of the earlier studies [33,38,40]. The key intermediate lactol **B** containing a lactol moiety is found as an equilibrium mixture with the corresponding hydroxyaldehyde **C**. Subsequently, the second Michael addition was conducted between the hydroxyaldehyde **C** and β-nitrostyrene **4g** in the presence of TEA, which occurs from *Si*-face attack followed by the Henry reaction providing the desired product **5g** as a single diastereoisomer, and obviously, the high stereoselectivity can be attributed to the directing effect of the primary chiral substituted groups in the structure. Therefore, the structure and stereochemistry of **5g** could be determined based on the relative configuration from the single-crystal X-ray analysis of racemate **5g** and combined with several known activation modes in the reaction of olefinic oxindole **1a** and aliphatic aldehydes driven by (*S*)-diphenylprolinol TMS ether **3** [33,38,40].



Scheme 2. Substrate scope for the [2+2+2] tandem reaction.



Scheme 3. One-pot, three-component tandem reaction to access spirocyclic oxindole.



Scheme 4. The detailed process of the one-pot, three-component [2+2+2] tandem reaction.

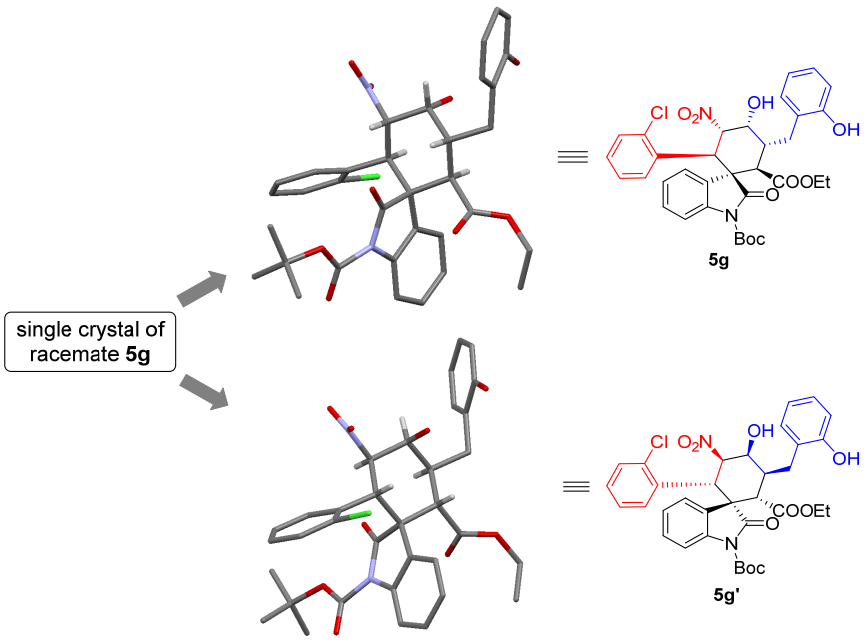


Figure 1. X-ray crystal structure of racemate **5g** and the hydrogen atoms (except those of the chiral centers) are omitted for clarity.

3. Materials and Methods

3.1. General Information

Reagents and solvents were purchased from commercial suppliers and used as received, without further purification. Chromatographic purification of products was accomplished using force-flow chromatography (FC) on silica gel (200–400 mesh). For thin layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF254, 0.25 mm) were used, using UV light as the visualizing agent and an acidic mixture of ceric ammonium molybdate or basic aqueous potassium permanganate ($KMnO_4$) as stain developing solutions. ^{1}H NMR spectra were obtained with a Bruker Avance 500 MHz spectrometer. Chemical shifts were reported in δ (ppm) units relative to tetramethylsilane (TMS) as the internal standard. ^{13}C NMR spectra were obtained at 125 MHz; chemical shifts were reported in ppm relative to TMS with the solvent resonance as the internal standard. Infrared spectra were obtained with a Bruker ALPHA-P spectrometer or a Perkin Elmer Spectrum One spectrometer. High resolution mass spectra (electron spray ionization) were obtained with a Bruker APEX IV Fourier-Transform mass spectrometer. Enantiomeric excesses (ee) were determined by chiral HPLC analysis using an Agilent 1200 LC instrument with a Daicel Chiralpak IA, IB or IC column and *i*-PrOH/*n*-hexane as the eluent was used. HPLC traces were compared with racemic samples prepared via mixing two enantiomeric final products, equally, obtained from (*S*) and (*R*) catalysts, respectively. (*S*) and (*R*)-Diphenylprolinol silyl ethers **3** are commercially available from Daicel chiral Technologies. All the cyclic hemiaminals, lactols and N-Boc-protected olefinic oxindole were synthesized according to literature procedures.

3.2. General Procedure for the One-Pot, [2+2+2] Tandem Reaction

To a mixture of **3** (0.005 mmol, 0.05 equiv) and *p*-nitrobenzoic acid (0.005 mmol, 0.05 equiv) in 0.4 mL EtOH (with 5% H_2O) was added olefinic oxindole **1** (0.1 mmol, 1 equiv), lactol **2** (0.12 mmol, 1.2 equiv) subsequently. The reaction was stirred at room temperature for 3 h, after which nitroolefin **4** was added followed by the addition of TEA (0.04 mmol 0.4 equiv). The reaction was kept in 25 °C for another 12 h. The product **5** was isolated by chromatography.

1′-(*tert*-butyl)2-ethyl(1*S*,2*R*,3*R*,4*R*,5*S*,6*R*)-4-hydroxy-3-(2-hydroxybenzyl)-5-nitro-2′-oxo-6-phenylspiro[cyclohexane-1,3′-indoline]-1′,2-dicarboxylate (5a): 88% yield; $[\alpha]_D^{25}$ = +52.6 (*c* = 1.0 in $CHCl_3$); 98% ee, determined by chiral HPLC analysis [Daicel Chiralcel IC, *n*-hexane/*i*-PrOH = 85/15, 1.0 mL/min, λ = 201 nm, t_{major} = 4.86 min, t_{minor} = 9.11 min]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 7.3, 1.2 Hz, 1H), 7.40 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.22–7.12 (m, 4H), 7.04–6.84 (m, 6H), 6.71–6.58 (m, 1H), 6.03 (dd, *J* = 12.3, 2.9 Hz, 1H), 4.40 (s, 1H), 4.13 (d, *J* = 12.3 Hz, 1H), 3.92–3.83 (m, 2H), 3.66 (d, *J* = 11.9 Hz, 1H), 3.40–3.34 (m, 1H), 3.08–3.02 (m, 1H), 2.46 (dd, *J* = 13.7, 4.4 Hz, 1H), 1.55 (s, 9H), 0.87 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.83, 171.38, 153.74, 148.43, 139.34, 133.02, 131.73, 129.03, 128.34, 127.86, 127.57, 124.39, 123.83, 122.83, 121.62, 115.82, 114.75, 85.94, 84.23, 68.24, 61.03, 54.68, 51.06, 46.62, 39.50, 29.42, 28.04, 13.62. ESI-HRMS: calcd. for $C_{34}H_{35}N_2O_9$ $[M-H]^-$ 615.2343, found 615.2340.

1′-(*tert*-butyl)2-ethyl(1*S*,2*R*,3*R*,4*R*,5*S*,6*R*)-6-(4-fluorophenyl)-4-hydroxy-3-(2-hydroxybenzyl)-5-nitro-2′-oxospiro[cyclohexane-1,3′-indoline]-1′,2-dicarboxylate (5b): 84% yield; $[\alpha]_D^{25}$ = +21.5 (*c* = 1.0 in $CHCl_3$); 97% ee, determined by chiral HPLC analysis [Daicel Chiralcel IC, *n*-hexane/*i*-PrOH = 85/15, 1.0 mL/min, λ = 201 nm, t_{major} = 4.39 min, t_{minor} = 8.38 min]; ^{1}H NMR (500 MHz, CD_3OD) δ 7.62 (d, *J* = 7.2 Hz, 1H), 7.39–7.35 (m, 1H), 7.29–7.19 (m, 2H), 7.14–7.04 (m, 2H), 6.84–6.52 (m, 5H), 5.87 (dd, *J* = 12.2, 2.7 Hz, 1H), 4.37 (s, 1H), 4.17 (d, *J* = 12.2 Hz, 1H), 3.79–3.71 (m, 2H), 3.58 (d, *J* = 12.2 Hz, 1H), 3.52–3.45 (m, 1H), 2.85–2.78 (m, 1H), 2.61 (dd, *J* = 13.4, 4.4 Hz, 1H), 1.55 (s, 8H), 0.84 (t, *J* = 7.1 Hz, 3H).^{13}C NMR (125 MHz, CD_3OD) δ 175.42, 171.43, 162.95, 161.33, 155.38, 148.48, 139.28, 131.03, 130.31, 128.87, 127.93, 127.58, 124.66, 124.49, 123.33, 119.41, 114.71, 114.38, 86.90, 84.36, 68.61, 60.64, 54.83, 51.35, 45.49, 38.12, 30.25, 26.93, 12.66. ESI-HRMS: calcd. for $C_{34}H_{34}FN_2O_9$ $[M-H]^-$ 633.2248, found 633.2243.

1′-(*tert*-butyl)2-ethyl(1*S*,2*R*,3*R*,4*R*,5*S*,6*R*)-2-(4-bromophenyl)-4-hydroxy-5-(2-hydroxybenzyl)-3-nitro-2′-oxospiro[cyclohexane-1,3′-indoline]-1′,6-dicarboxylate (5c): 86% yield; $[\alpha]_D^{25}$ = +65.7 (*c* = 1.0 in $CHCl_3$); 97% ee, determined by chiral HPLC analysis [Daicel Chiralcel IC, *n*-hexane/*i*-PrOH = 85/15, 1.0 mL/min, λ = 201 nm, t_{major} = 4.50 min, t_{minor} = 9.20 min]; ^{1}H NMR (500 MHz, CD_3OD) *δ* 7.64–7.59 (m, 1H), 7.37 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.30–7.21 (m, 2H), 7.18–6.95 (m, 4H), 6.79 (dd, *J* = 13.7, 7.4 Hz, 2H), 6.64–6.31 (m, 1H), 5.86 (dd, *J* = 12.1, 2.8 Hz, 1H), 4.38 (s, 1H), 4.15 (d, *J* = 12.1 Hz, 1H), 3.79–3.71 (m, 2H), 3.58 (d, *J* = 12.2 Hz, 1H), 3.53–3.44 (m, 1H), 2.85–2.78 (m, 1H), 2.62 (dd, *J* = 13.4, 4.4 Hz, 1H), 1.55 (s, 7H), 0.84 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, CD_3OD) *δ* 175.37, 171.41, 163.55, 155.39, 148.39, 139.28, 133.69, 131.03, 130.62, 128.97, 127.80, 127.59, 124.65, 124.54, 123.35, 121.31, 119.41, 114.71, 114.47, 86.64, 84.44, 68.62, 60.66, 54.71, 51.26, 45.72, 38.13, 30.26, 26.94, 12.66. ESI-HRMS: calcd. for $C_{34}H_{34}BrN_2O_9$ $[M-H]^-$ 693.1448, found 693.1451.

1′-(*tert*-butyl)2-ethyl(1*S*,2*R*,3*R*,4*R*,5*S*,6*R*)-4-hydroxy-3-(2-hydroxybenzyl)-6-(4-methoxyphenyl)-5-nitro-2′-oxospiro[cyclohexane-1,3′-indoline]-1′,2-dicarboxylate (5d): 75% yield; $[\alpha]_D^{25}$ = +56.3 (*c* = 1.0 in $CHCl_3$); 95% ee, determined by chiral HPLC analysis [Daicel Chiralcel IC, *n*-hexane/*i*-PrOH = 85/15, 1.0 mL/min, λ = 201 nm, t_{major} = 5.76 min, t_{minor} = 12.08 min]; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.47–7.42 (m, 2H), 7.22–7.12 (m, 4H), 6.93 (dd, *J* = 10.7, 4.1 Hz, 1H), 6.84 (d, *J* = 7.7 Hz, 1H), 6.57–6.40 (m, 3H), 5.98 (dd, *J* = 12.3, 2.7 Hz, 1H), 4.37 (s, 1H), 4.10–4.02 (m, 2H), 3.92–3.82 (m, 2H), 3.62 (s, 3H), 3.38–3.29 (m, 1H), 3.07–2.99 (m, 1H), 2.45 (dd, *J* = 13.7, 4.4 Hz, 1H), 1.57 (s, 8H), 0.87 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 174.91, 171.29, 158.97, 153.79, 148.45, 139.40, 131.71, 129.00, 128.35, 127.70, 124.75, 124.37, 123.79, 122.73, 121.63, 115.91, 114.87, 113.33, 86.17, 84.18, 68.08, 61.05, 54.98, 54.73, 51.07, 45.98, 39.39, 28.06, 13.62. ESI-HRMS: calcd. for $C_{35}H_{37}N_2O_{10}$ $[M-H]^-$ 645.2448, found 645.2450.

1′-(*tert*-butyl)2-ethyl(1*S*,2*R*,3*R*,4*R*,5*S*,6*R*)-6-(4-cyanophenyl)-4-hydroxy-3-(2-hydroxybenzyl)-5-nitro-2′-oxospiro[cyclohexane-1,3′-indoline]-1′,2-dicarboxylate (5e): 75% yield; $[\alpha]_D^{25}$ = +83.2 (*c* = 1.0 in $CHCl_3$); 99% ee, determined by chiral HPLC analysis [Daicel Chiralcel IC, *n*-hexane/*i*-PrOH = 85/15, 1.0 mL/min, λ = 201 nm, t_{major} = 10.29 min, t_{minor} = 19.55 min]; ^{1}H NMR (500 MHz, CD_3OD) *δ* 7.65 (d, *J* = 7.0 Hz, 1H), 7.48–7.18 (m, 6H), 7.15–7.05 (m, 2H), 6.80 (dd, *J* = 13.9, 7.5 Hz, 2H), 5.94 (dd, *J* = 12.1, 2.8 Hz, 1H), 4.43 (s, 1H), 4.28 (d, *J* = 12.1 Hz, 1H), 3.80–3.70 (m, 2H), 3.60 (d, *J* = 12.1 Hz, 1H), 3.53–3.45 (m, 1H), 2.84–2.79 (m, 1H), 2.63 (dd, *J* = 13.4, 4.4 Hz, 1H), 1.55 (s, 9H), 0.84 (t, *J* = 7.1 Hz, 3H).^{13}C NMR (125 MHz, CD_3OD) *δ* 175.00, 171.27, 163.55, 155.39, 148.35, 140.46, 139.16, 131.03, 129.15, 127.62, 127.39, 124.64, 124.61, 123.47, 119.43, 117.80, 114.72, 114.42, 111.26, 86.42, 84.57, 68.64, 60.72, 54.69, 51.41, 46.24, 38.14, 30.24, 26.93, 12.66. ESI-HRMS: calcd. For $C_{35}H_{34}N_3O_9$ $[M-H]^-$ 640.2295, found 640.2291.

1′-(*tert*-butyl)2-ethyl(1*S*,2*R*,3*R*,4*R*,5*S*,6*R*)-4-hydroxy-3-(2-hydroxybenzyl)-5-nitro-2′-oxo-6-(p-tolyl)spiro[cyclohexane-1,3′-indoline]-1′,2-dicarboxylate (5f): 75% yield; $[\alpha]_D^{25}$ = +59.7 (*c* = 1.0 in $CHCl_3$); 95% ee, determined by chiral HPLC analysis [Daicel Chiralcel IC, *n*-hexane/*i*-PrOH = 85/15, 1.0 mL/min, λ = 201 nm, t_{major} = 4.92 min, t_{minor} = 9.40 min]; ^{1}H NMR (500 MHz, CD_3OD) *δ* 7.60 (d, *J* = 7.3 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.28–7.17 (m, 2H), 7.14–7.04 (m, 2H), 6.85–6.67 (m, 4H), 5.90–5.84 (m, 1H), 4.35 (s, 1H), 4.11 (d, *J* = 12.2 Hz, 1H), 3.79–3.69 (m, 2H), 3.57 (d, *J* = 12.1 Hz, 1H), 3.53–3.45 (m, 1H), 2.82 (dd, *J* = 13.4, 10.1 Hz, 1H), 2.60 (dd, *J* = 13.4, 4.4 Hz, 1H), 2.12 (s, 3H), 1.54 (s, 8H), 0.83 (t, *J* = 7.1 Hz, 3H).^{13}C NMR (125 MHz, CD_3OD) *δ* 175.48, 171.40, 155.24, 148.43, 139.24, 137.05, 130.91, 128.55, 128.11, 128.02, 127.44, 124.59, 124.22, 123.16, 119.30, 114.60, 114.26, 86.86, 84.05, 68.50, 60.47, 54.74, 51.30, 45.72, 38.05, 30.14, 26.85, 19.50, 12.55. ESI-HRMS: calcd. For $C_{35}H_{37}N_2O_9$ $[M-H]^-$ 629.2499, found 629.2498.

1′-(*tert*-butyl)2-ethyl(1*S*,2*R*,3*R*,4*R*,5*S*,6*R*)-6-(2-chlorophenyl)-4-hydroxy-3-(2-hydroxybenzyl)-5-nitro-2′-oxospiro[cyclohexane-1,3′-indoline]-1′,2-dicarboxylate (5g): 71% yield; $[\alpha]_D^{25}$ = +27.8 (*c* = 1.0 in $CHCl_3$); 96% ee, determined by chiral HPLC analysis [Daicel Chiralcel IC, *n*-hexane/*i*-PrOH = 85/15, 1.0 mL/min, λ = 201 nm, t_{major} = 4.83 min, t_{minor} = 10.62 min]; ^{1}H NMR (500 MHz, CD_3OD) *δ* 7.68–7.64 (m, 1H), 7.34 (dd, *J* = 12.0, 4.8 Hz, 2H), 7.20–7.01 (m, 7H), 6.80 (dd, *J* = 13.2, 7.2 Hz, 2H), 5.83 (dd, *J* = 12.0, 2.7 Hz, 1H), 5.01 (d, *J* = 12.0 Hz, 1H), 4.38 (s, 1H), 3.78–3.69 (m, 2H), 3.62 (d, *J* = 12.1 Hz, 1H), 3.58–3.51 (m, 1H), 2.86–2.81 (m, 1H), 2.61 (dd, *J* = 13.4, 4.3 Hz, 1H), 1.59 (s, 9H), 0.83 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, CD_3OD) *δ* 175.83, 171.35, 163.55, 155.37, 148.61, 138.93, 135.87, 132.98,

131.03, 129.64, 128.88, 128.69, 127.57, 126.97, 126.39, 125.14, 124.71, 123.77, 119.42, 114.71, 113.72, 87.64, 84.43, 68.68, 60.63, 54.60, 51.89, 40.53, 38.13, 30.23, 27.00, 12.64. ESI-HRMS: calcd. for $C_{34}H_{34}ClN_2O_9$ $[M - H]^-$ 649.1953, found 649.1957.

1′-(*tert*-butyl)2-ethyl(1*S*,2*R*,3*R*,4*R*,5*S*,6*R*)-4-hydroxy-3-(2-hydroxybenzyl)-6-(3-methoxyphenyl)-5-nitro-2′-oxospiro[cyclohexane-1,3′-indoline]-1′,2-dicarboxylate (5h): 79% yield; $[\alpha]_D^{25}$ = +57.2 (*c* = 1.0 in $CHCl_3$); 93% ee, determined by chiral HPLC analysis [Daicel Chiralcel IC, *n*-hexane/*i*-PrOH = 85/15, 1.0 mL/min, λ = 201 nm, t_{major} = 4.33 min, t_{minor} = 7.09 min]; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.46 (t, *J* = 8.3 Hz, 2H), 7.23–7.10 (m, 4H), 6.98–6.80 (m, 3H), 6.57 (d, *J* = 8.2 Hz, 1H), 6.38 (s, 1H), 6.00 (d, *J* = 12.3 Hz, 1H), 4.38 (s, 1H), 4.14–4.07 (m, 1H), 3.92–3.81 (m, 2H), 3.65 (d, *J* = 11.9 Hz, 1H), 3.58–3.42 (m, 3H), 3.36 (t, *J* = 10.5 Hz, 1H), 3.04 (t, *J* = 12.8 Hz, 1H), 2.46 (dd, *J* = 13.6, 3.8 Hz, 1H), 1.55 (s, 8H), 0.90–0.84 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 174.69, 171.27, 153.67, 148.47, 139.52, 134.40, 131.73, 129.07, 128.81, 128.36, 127.68, 124.29, 123.79, 122.76, 121.70, 115.84, 114.88, 85.91, 84.23, 68.20, 61.08, 54.91, 54.60, 51.06, 46.65, 39.43, 29.38, 27.97, 13.62. ESI-HRMS: calcd. for $C_{35}H_{37}N_2O_{10}$ $[M - H]^-$ 645.2448, found 645.24544.

1′-(*tert*-butyl)2-ethyl(1*S*,2*R*,3*R*,4*R*,5*S*,6*R*)-4-hydroxy-3-(2-hydroxybenzyl)-6-(naphthalen-2-yl)-5-nitro-2′-oxospiro[cyclohexane-1,3′-indoline]-1′,2-dicarboxylate (5i): 72% yield; $[\alpha]_D^{25}$ = +109.8 (*c* = 1.0 in $CHCl_3$); 97% ee, determined by chiral HPLC analysis [Daicel Chiralcel IC, *n*-hexane/*i*-PrOH = 85/15, 1.0 mL/min, λ = 201 nm, t_{major} = 5.93 min, t_{minor} = 9.89 min]; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.68–7.51 (m, 3H), 7.40–7.27 (m, 3H), 7.24–7.09 (m, 4H), 6.96 (t, *J* = 7.4 Hz, 1H), 6.85 (d, *J* = 8.0 Hz, 1H), 6.77–6.56 (m, 1H), 6.30 (s, 1H), 6.21–6.13 (m, 1H), 4.44 (s, 1H), 4.30 (d, *J* = 12.2 Hz, 1H), 4.06 (s, 1H), 3.94–3.81 (m, 2H), 3.71 (d, *J* = 11.9 Hz, 1H), 3.43 (t, *J* = 10.5 Hz, 1H), 3.07 (t, *J* = 12.8 Hz, 1H), 2.49 (dd, *J* = 13.7, 4.1 Hz, 1H), 1.39 (s, 8H), 0.90–0.85 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 174.82, 171.26, 153.69, 148.26, 139.35, 132.73, 132.64, 131.75, 129.10, 128.38, 127.97, 127.52, 127.31, 126.08, 125.87, 124.38, 123.81, 122.82, 121.73, 115.87, 114.82, 86.18, 84.16, 68.26, 61.09, 54.77, 51.21, 41.95, 39.48, 29.42, 27.87, 13.62. ESI-HRMS: calcd. for $C_{38}H_{37}N_2O_9$ $[M - H]^-$ 665.2499, found 665.2494.

1′-(*tert*-butyl)2-ethyl(1*S*,2*R*,3*R*,4*R*,5*S*,6*R*)-6-(furan-2-yl)-4-hydroxy-3-(2-hydroxybenzyl)-5-nitro-2'-oxospiro[cyclohexane-1,3′-indoline]-1′,2-dicarboxylate (5j): 81% yield; $[\alpha]_D^{25}$ = +42.7 (*c* = 1.0 in $CHCl_3$); 97% ee, determined by chiral HPLC analysis [Daicel Chiralcel IC, *n*-hexane/*i*-PrOH = 85/15, 1.0 mL/min, λ = 201 nm, t_{major} = 9.20 min, t_{minor} = 11.41 min]; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.57 (d, *J* = 7.7 Hz, 1H), 7.45–7.41 (m, 1H), 7.28–7.19 (m, 2H), 7.16–7.11 (m, 2H), 7.00 (d, *J* = 1.0 Hz, 1H), 6.93 (dd, *J* = 15.4, 8.0 Hz, 1H), 6.86–6.81 (m, 1H), 6.00 (dd, *J* = 3.2, 1.8 Hz, 1H), 5.89 (dd, *J* = 12.1, 2.9 Hz, 1H), 5.72 (d, *J* = 3.3 Hz, 1H), 4.37 (s, 1H), 4.30 (d, *J* = 12.1 Hz, 1H), 3.93–3.83 (m, 2H), 3.56 (d, *J* = 11.9 Hz, 1H), 3.33–3.24 (m, 1H), 3.05–2.97 (m, 1H), 2.42 (dd, *J* = 13.6, 4.4 Hz, 1H), 1.59 (s, 8H), 0.88 (q, *J* = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 174.40, 171.13, 153.59, 148.71, 148.24, 142.04, 139.57, 131.76, 129.19, 128.34, 127.73, 124.60, 123.76, 122.79, 121.72, 115.73, 114.86, 110.12, 108.17, 85.06, 84.31, 67.94, 61.12, 53.76, 50.91, 41.10, 39.40, 29.25, 28.05, 13.63. ESI-HRMS: calcd. for $C_{32}H_{33}N_2O_{10}$ $[M - H]^-$ 605.2135, found 605.2136.

1′-(*tert*-butyl)2-ethyl(1*S*,2*R*,3*R*,4*R*,5*S*,6*R*)-4-hydroxy-3-(2-hydroxybenzyl)-5-nitro-2′-oxo-6-(thiophen-2-yl)spiro[cyclohexane-1,3′-indoline]-1′,2-dicarboxylate (5k): 81% yield; $[\alpha]_D^{25}$ = +46.6 (*c* = 1.0 in $CHCl_3$); 96% ee, determined by chiral HPLC analysis [Daicel Chiralcel IC, *n*-hexane/*i*-PrOH = 85/15, 1.0 mL/min, λ = 201 nm, t_{major} = 5.15 min, t_{minor} = 8.72 min]; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.54–7.50 (m, 1H), 7.45 (dd, *J* = 8.3, 4.9 Hz, 1H), 7.24 (dd, *J* = 5.6, 3.4 Hz, 2H), 7.14 (t, *J* = 6.7 Hz, 2H), 6.93 (dd, *J* = 13.5, 6.2 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 1H), 6.71–6.65 (m, 2H), 5.93 (dd, *J* = 12.0, 2.7 Hz, 1H), 4.40–4.34 (m, 2H), 3.93–3.83 (m, 2H), 3.61 (d, *J* = 11.9 Hz, 1H), 3.35–3.27 (m, 1H), 3.05–2.98 (m, 1H), 2.43 (dd, *J* = 13.6, 4.4 Hz, 1H), 1.57 (s, 9H), 0.88 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 174.78, 171.19, 153.64, 148.55, 139.72, 135.62, 131.74, 129.32, 128.37, 127.84, 126.13, 125.63, 125.23, 124.68, 123.73, 122.71, 121.69, 115.76, 114.96, 87.16, 84.32, 68.11, 61.13, 54.99, 51.06, 42.04, 39.34, 29.29, 28.04, 13.63. ESI-HRMS: calcd. for $C_{32}H_{33}N_2O_9S$ $[M - H]^-$ 621.1907, found 621.1909.

1′-(*tert*-butyl)2-ethyl(1*S*,2*R*,3*R*,4*R*,5*S*,6*R*)-2-(1-(*tert*-butoxycarbonyl)-1H-indol-3-yl)-4-hydroxy-5-(2-hydroxybenzyl)-3-nitro-2′-oxospiro[cyclohexane-1,3′-indoline]-1′,6-dicarboxylate (5l): 99% yield; $[\alpha]_D^{25}$ = +53.7 (*c* = 1.0 in $CHCl_3$); 92% ee, determined by chiral HPLC analysis [Daicel Chiralcel IC, *n*-hexane/*i*-PrOH = 85/15, 1.0 mL/min, λ = 201 nm, t_{major} = 4.46 min, t_{minor} = 8.30 min]; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.81 (s, 1H), 7.55 (d, *J* = 7.4 Hz, 1H), 7.49 (s, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 9.1 Hz, 1H), 7.15 (dd, *J* = 12.1, 7.6 Hz, 2H), 7.09 (t, *J* = 7.5 Hz, 2H), 7.04–6.92 (m, 3H), 6.83 (d, *J* = 7.9 Hz, 1H), 6.31 (s, 1H), 5.90 (d, *J* = 12.2 Hz, 1H), 4.52 (d, *J* = 12.2 Hz, 1H), 4.36 (s, 1H), 4.06 (d, *J* = 6.9 Hz, 1H), 3.92–3.81 (m, 2H), 3.68 (d, *J* = 11.9 Hz, 1H), 3.33 (t, *J* = 9.9 Hz, 1H), 3.06 (t, *J* = 12.8 Hz, 1H), 2.45 (dd, *J* = 13.6, 3.9 Hz, 1H), 1.60 (d, *J* = 2.5 Hz, 15H), 0.88 (t, *J* = 7.1 Hz, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 175.29, 171.20, 153.59, 149.22, 148.69, 139.31, 131.75, 130.00, 129.19, 128.37, 127.50, 124.36, 124.31, 123.79, 123.30, 122.86, 122.06, 121.73, 118.65, 115.79, 114.87, 114.75, 114.58, 87.64, 84.34, 83.95, 68.01, 61.10, 54.67, 51.58, 39.42, 36.67, 29.27, 28.10, 28.01, 13.61. ESI-HRMS: calcd. for $C_{41}H_{44}N_3O_{11}$ $[M-H]^-$ 754.2976, found 754.2977.

1′-(*tert*-butyl)2-ethyl(1*S*,2*R*,3*R*,4*R*,5*S*,6*R*)-5′-bromo-4-hydroxy-3-(2-hydroxybenzyl)-5-nitro-2′-oxo-6-phenylspiro[cyclohexane-1,3′-indoline]-1′,2-dicarboxylate (5m): 77% yield; $[\alpha]_D^{25}$ = +33.8 (*c* = 1.0 in $CHCl_3$); 96% ee, determined by chiral HPLC analysis [Daicel Chiralcel IC, *n*-hexane/*i*-PrOH = 85/15, 1.0 mL/min, λ = 201 nm, t_{major} = 5.27 min, t_{minor} = 10.20 min]; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.61 (s, 1H), 7.31 (q, *J* = 8.7 Hz, 2H), 7.16 (t, *J* = 7.2 Hz, 2H), 7.08–6.93 (m, 4H), 6.84 (d, *J* = 8.2 Hz, 1H), 6.30 (s, 1H), 5.97 (dd, *J* = 12.2, 2.0 Hz, 1H), 4.38 (s, 1H), 4.08 (d, *J* = 12.1 Hz, 1H), 3.99–3.84 (m, 2H), 3.61 (d, *J* = 11.9 Hz, 1H), 3.33 (dd, *J* = 11.6, 9.2 Hz, 1H), 3.03 (dd, *J* = 24.0, 11.7 Hz, 1H), 2.47 (dd, *J* = 13.6, 3.9 Hz, 1H), 1.55 (s, 8H), 0.94–0.86 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 173.91, 171.20, 153.61, 148.19, 138.51, 132.60, 132.01, 131.76, 129.89, 128.44, 128.09, 128.07, 125.88, 123.67, 121.76, 85.70, 84.59, 68.08, 61.21, 54.72, 50.82, 46.58, 39.49, 29.36, 28.01, 13.69. ESI-HRMS: calcd. for $C_{34}H_{34}BrN_2O_9$ $[M-H]^-$ 693.1448, found 693.1446.

1′-(*tert*-butyl)2-ethyl(1*S*,2*R*,3*R*,4*R*,5*S*,6*R*)-5′-chloro-4-hydroxy-3-(2-hydroxybenzyl)-5-nitro-2′-oxo-6-phenylspiro[cyclohexane-1,3′-indoline]-1′,2-dicarboxylate (5n): 82% yield; $[\alpha]_D^{25}$ = +103.8 (*c* = 1.0 in $CHCl_3$); 98% ee, determined by chiral HPLC analysis [Daicel Chiralcel IC, *n*-hexane/*i*-PrOH = 85/15, 1.0 mL/min, λ = 201 nm, t_{major} = 5.99 min, t_{minor} = 11.37 min]; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.48 (d, *J* = 1.7 Hz, 1H), 7.38 (d, *J* = 8.7 Hz, 1H), 7.16 (t, *J* = 8.0 Hz, 3H), 7.08–6.92 (m, 4H), 6.84 (d, *J* = 7.8 Hz, 1H), 6.29 (s, 1H), 5.98 (dd, *J* = 12.2, 2.2 Hz, 1H), 4.37 (d, *J* = 13.9 Hz, 1H), 4.09 (d, *J* = 12.5 Hz, 2H), 3.97–3.85 (m, 2H), 3.62 (d, *J* = 11.9 Hz, 1H), 3.38–3.30 (m, 1H), 3.04 (t, *J* = 12.8 Hz, 1H), 1.55 (s, 8H), 0.92 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 174.05, 171.18, 153.62, 137.99, 132.63, 131.75, 129.88, 129.56, 129.09, 128.43, 128.07, 123.67, 123.02, 121.75, 116.11, 115.82, 85.73, 84.57, 68.09, 61.20, 54.77, 50.83, 46.57, 39.49, 29.37, 28.02, 13.68. ESI-HRMS: calcd. for $C_{34}H_{34}ClN_2O_9$ $[M-H]^-$ 649.1953, found 649.1957.

1′-(*tert*-butyl)2-ethyl(1*S*,2*R*,3*R*,4*R*,5*S*,6*R*)-4-hydroxy-3-(2-hydroxybenzyl)-5′-methoxy-5-nitro-2′-oxo-6-phenylspiro[cyclohexane-1,3′-indoline]-1′,2-dicarboxylate (5o): 65% yield; $[\alpha]_D^{25}$ = +88.8 (*c* = 1.0 in $CHCl_3$); 92% ee, determined by chiral HPLC analysis [Daicel Chiralcel IC, *n*-hexane/*i*-PrOH = 85/15, 1.0 mL/min, λ = 201 nm, t_{major} = 5.45 min, t_{minor} = 15.19 min]; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.26 (d, *J* = 2.5 Hz, 1H), 7.15 (t, *J* = 8.1 Hz, 2H), 7.05–6.91 (m, 5H), 6.85 (d, *J* = 7.8 Hz, 1H), 6.38 (s, 1H), 6.02 (dd, *J* = 12.3, 2.2 Hz, 1H), 4.38 (s, 1H), 4.11–4.04 (m, 2H), 3.64 (d, *J* = 11.9 Hz, 1H), 3.40–3.30 (m, 1H), 3.04 (t, *J* = 12.8 Hz, 1H), 2.47 (dd, *J* = 13.7, 4.2 Hz, 1H), 2.39 (s, 3H), 1.54 (s, 7H), 0.87 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 174.90, 171.25, 153.73, 148.46, 137.00, 134.04, 132.94, 131.74, 129.53, 128.36, 127.85, 127.45, 123.81, 123.24, 121.68, 115.87, 114.56, 85.98, 84.00, 68.18, 61.02, 54.66, 51.05, 46.68, 39.41, 29.42, 28.05, 21.12, 13.61.. ESI-HRMS: calcd. for $C_{35}H_{37}N_2O_{10}$ $[M-H]^-$ 645.2448, found 645.2448.

1′-(*tert*-butyl)2-ethyl(1*S*,2*R*,3*R*,4*R*,5*S*,6*R*)-5′-fluoro-4-hydroxy-3-(2-hydroxybenzyl)-5-nitro-2′-oxo-6-phenylspiro[cyclohexane-1,3′-indoline]-1′,2-dicarboxylate (5p): 65% yield; $[\alpha]_D^{25}$ = +47.8 (*c* = 1.0 in $CHCl_3$); 94% ee, determined by chiral HPLC analysis [Daicel Chiralcel IC, *n*-hexane/*i*-PrOH = 85/15, 1.0 mL/min, λ = 201 nm, t_{major} = 5.31 min, t_{minor} = 11.33 min]; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.41 (dd,

J = 8.9, 4.4 Hz, 1H), 7.21 (dd, *J* = 7.5, 2.3 Hz, 1H), 7.16 (t, *J* = 7.4 Hz, 2H), 7.07–6.93 (m, 4H), 6.90–6.82 (m, 2H), 6.30 (s, 1H), 5.99 (dd, *J* = 12.2, 2.4 Hz, 1H), 4.38 (s, 1H), 4.08 (dd, *J* = 12.5, 5.1 Hz, 2H), 3.96–3.85 (m, 2H), 3.60 (d, *J* = 11.9 Hz, 1H), 3.35 (td, *J* = 11.9, 2.8 Hz, 1H), 3.08–3.00 (m, 1H), 2.46 (dd, *J* = 13.7, 4.3 Hz, 1H), 1.55 (s, 8H), 0.92 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.80, 171.22, 153.59, 147.88, 144.77, 144.37, 132.40, 131.76, 129.50, 128.49, 128.32, 128.23, 125.37, 123.58, 121.80, 118.39, 115.69, 115.00, 85.50, 68.04, 65.90, 61.40, 54.68, 50.75, 46.46, 39.67, 29.37, 27.98, 13.77. ESI-HRMS: calcd. for $C_{34}H_{34}FN_2O_9$ $[M-H]^-$ 633.2248, found 633.2243.

1′-(*tert*-butyl)2-ethyl(1*S*,2*R*,3*R*,4*R*,5*S*,6*R*)-4-hydroxy-3-(2-hydroxybenzyl)-5,5′-dinitro-2′-oxo-6-phenylspiro[cyclohexane-1,3′-indoline]-1′,2-dicarboxylate (5q): 39% yield; $[\alpha]_D^{25}$ = +136.5 (*c* = 1.0 in $CHCl_3$); 98% ee, determined by chiral HPLC analysis [Daicel Chiralcel IC, *n*-hexane/*i*-PrOH = 85/15, 1.0 mL/min, λ = 201 nm, t_{major} = 6.39 min, t_{minor} = 15.73 min]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (d, *J* = 2.0 Hz, 1H), 8.12 (dd, *J* = 9.0, 2.1 Hz, 1H), 7.61 (d, *J* = 9.0 Hz, 1H), 7.17 (t, *J* = 7.5 Hz, 2H), 7.10–6.93 (m, 4H), 6.84 (d, *J* = 7.9 Hz, 1H), 5.94 (dd, *J* = 12.2, 2.5 Hz, 1H), 4.41 (s, 1H), 4.18 (d, *J* = 12.2 Hz, 2H), 3.90 (q, *J* = 7.1 Hz, 2H), 3.73 (t, *J* = 11.1 Hz, 1H), 3.34 (td, *J* = 11.8, 2.7 Hz, 1H), 3.07 (t, *J* = 12.8 Hz, 1H), 2.48 (dd, *J* = 13.6, 4.3 Hz, 1H), 1.58 (s, 9H), 0.91 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.34, 171.16, 160.75, 158.81, 153.62, 148.35, 135.39, 132.68, 131.75, 129.57, 129.51, 128.42, 128.07, 128.03, 123.68, 121.76, 116.32, 116.25, 115.82, 115.76, 115.58, 110.37, 110.17, 85.75, 84.43, 68.09, 61.21, 54.90, 50.90, 46.60, 39.51, 29.35, 28.03, 13.68. ESI-HRMS: calcd. for $C_{34}H_{34}N_3O_{11}$ $[M-H]^-$ 660.2193, found 660.2195.

1′-(*tert*-butyl)2-ethyl(1*S*,2*R*,3*R*,4*R*,5*S*,6*R*)-7′-bromo-4-hydroxy-3-(2-hydroxybenzyl)-5-nitro-2′-oxo-6-phenylspiro[cyclohexane-1,3′-indoline]-1′,2-dicarboxylate (5r): 71% yield; $[\alpha]_D^{25}$ = +21.3 (*c* = 1.0 in $CHCl_3$); 98% ee, determined by chiral HPLC analysis [Daicel Chiralcel IC, *n*-hexane/*i*-PrOH = 85/15, 1.0 mL/min, λ = 201 nm, t_{major} = 4.60 min, t_{minor} = 10.12 min]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.4 Hz, 1H), 7.34 (d, *J* = 8.1 Hz, 1H), 7.16 (t, *J* = 6.9 Hz, 2H), 7.10–6.93 (m, 5H), 6.83 (d, *J* = 8.2 Hz, 1H), 6.09 (s, 1H), 6.04 (dd, *J* = 12.2, 2.2 Hz, 1H), 4.37 (s, 1H), 4.14 (d, *J* = 12.2 Hz, 1H), 4.01–3.85 (m, 3H), 3.58 (d, *J* = 11.9 Hz, 1H), 3.27 (dd, *J* = 11.9, 9.4 Hz, 1H), 3.01 (t, *J* = 12.8 Hz, 1H), 2.44 (dd, *J* = 13.7, 4.1 Hz, 1H), 1.56 (s, 8H), 0.96–0.90 (m, 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ 174.54, 170.50, 153.60, 150.83, 146.72, 138.28, 133.79, 132.48, 131.74, 131.16, 128.42, 128.14, 125.25, 123.65, 122.14, 121.77, 115.87, 106.21, 85.77, 85.15, 68.00, 61.40, 55.68, 51.28, 46.38, 39.38, 29.27, 27.66, 13.61. ESI-HRMS: calcd. for $C_{34}H_{34}BrN_2O_9$ $[M-H]^-$ 693.1448, found 693.1449.

1′-(*tert*-butyl)2-ethyl(1*S*,2*R*,3*R*,4*R*,5*S*,6*R*)-3-(5-fluoro-2-hydroxybenzyl)-4-hydroxy-5-nitro-2′-oxo-6-phenylspiro[cyclohexane-1,3′-indoline]-1′,2-dicarboxylate (5s): 81% yield; $[\alpha]_D^{25}$ = +51.2 (*c* = 1.0 in $CHCl_3$); 97% ee, determined by chiral HPLC analysis [Daicel Chiralcel IC, *n*-hexane/*i*-PrOH = 85/15, 1.0 mL/min, λ = 201 nm, t_{major} = 4.53 min, t_{minor} = 7.64 min]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.1 Hz, 1H), 7.40 (d, *J* = 7.7 Hz, 1H), 7.23–7.14 (m, 2H), 7.06–6.77 (m, 7H), 6.65 (s, 1H), 6.05 (dd, *J* = 12.3, 2.0 Hz, 1H), 4.39 (s, 1H), 4.14–4.04 (m, 2H), 3.92–3.81 (m, 2H), 3.65 (d, *J* = 11.9 Hz, 1H), 3.41–3.32 (m, 1H), 3.02 (t, *J* = 12.7 Hz, 1H), 2.43 (dd, *J* = 13.6, 4.2 Hz, 1H), 1.55 (s, 8H), 0.86 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.79, 171.22, 158.28, 156.37, 149.92, 149.91, 148.40, 139.33, 132.77, 129.10, 127.95, 127.90, 127.44, 125.52, 125.46, 124.42, 122.79, 117.78, 117.60, 116.86, 116.79, 114.79, 114.60, 85.91, 84.34, 68.16, 61.19, 54.63, 50.94, 46.68, 39.20, 29.67, 28.03, 13.58. ESI-HRMS: calcd. for $C_{34}H_{34}FN_2O_9$ $[M-H]^-$ 633.2248, found 633.2245.

1′-(*tert*-butyl)2-ethyl(1*S*,2*R*,3*R*,4*R*,5*S*,6*R*)-3-(4-chloro-2-hydroxybenzyl)-4-hydroxy-5-nitro-2′-oxo-6-phenylspiro[cyclohexane-1,3′-indoline]-1′,2-dicarboxylate (5t): 63% yield; $[\alpha]_D^{25}$ = +33.9 (*c* = 1.0 in $CHCl_3$); 92% ee, determined by chiral HPLC analysis [Daicel Chiralcel IC, *n*-hexane/*i*-PrOH = 85/15, 1.0 mL/min, λ = 201 nm, t_{major} = 4.36 min, t_{minor} = 7.11 min]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (t, *J* = 8.8 Hz, 1H), 7.38 (d, *J* = 7.9 Hz, 1H), 7.23–7.15 (m, 2H), 7.10–6.85 (m, 7H), 6.06–6.00 (m, 1H), 4.38 (d, *J* = 21.5 Hz, 1H), 4.16–4.03 (m, 2H), 3.93–3.79 (m, 2H), 3.65 (d, *J* = 11.9 Hz, 1H), 3.36 (td, *J* = 11.8, 2.8 Hz, 1H), 3.06–2.96 (m, 1H), 2.45 (dd, *J* = 13.7, 4.3 Hz, 1H), 1.55 (s, 8H), 0.86 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.04, 171.39, 154.83, 148.37, 139.26, 133.16, 132.83, 132.43, 129.11, 127.93, 127.48, 124.49, 122.85, 122.63, 121.45, 116.27, 114.80, 85.92, 84.48, 68.18, 61.22, 54.70, 50.99, 46.65, 39.20, 29.14, 28.02, 13.59. ESI-HRMS: calcd. for $C_{34}H_{34}ClN_2O_9$ $[M-H]^-$ 649.1953, found 649.1951.

1′-(*tert*-butyl)2-ethyl(1*S*,2*R*,3*R*,4*R*,5*S*,6*R*)-4-hydroxy-3-(2-hydroxy-5-methoxybenzyl)-5-nitro-2′-oxo-6-phenylspiro[cyclohexane-1,3′-indoline]-1′,2-dicarboxylate (5u): 73% yield; $[\alpha]_D^{25}$ = +71.4 (*c* = 1.0 in $CHCl_3$); 99% ee, determined by chiral HPLC analysis [Daicel Chiralcel IC, *n*-hexane/*i*-PrOH = 85/15, 1.0 mL/min, λ = 201 nm, t_{major} = 6.91 min, t_{minor} = 13.76 min]; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.47 (d, *J* = 7.2 Hz, 1H), 7.41 (d, *J* = 7.7 Hz, 1H), 7.22–7.13 (m, 2H), 7.06–6.88 (m, 4H), 6.78 (d, *J* = 9.2 Hz, 1H), 6.70 (d, *J* = 7.0 Hz, 2H), 6.12 (s, 1H), 6.02 (dt, *J* = 11.8, 5.9 Hz, 1H), 4.39 (s, 1H), 4.20 (s, 1H), 4.11 (d, *J* = 12.3 Hz, 1H), 3.91–3.83 (m, 2H), 3.79 (s, 3H), 3.65 (d, *J* = 11.9 Hz, 1H), 3.37 (td, *J* = 11.7, 3.4 Hz, 1H), 3.03 (t, *J* = 12.8 Hz, 1H), 2.42 (dd, *J* = 13.6, 4.4 Hz, 1H), 1.56 (s, 8H), 0.87 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 174.79, 171.30, 154.30, 148.41, 147.48, 139.40, 132.94, 129.04, 127.88, 127.55, 124.74, 124.35, 122.76, 116.69, 116.28, 114.77, 113.92, 85.89, 84.17, 68.24, 61.06, 55.83, 54.63, 51.00, 46.64, 39.45, 29.72, 28.04, 13.63.ESI-HRMS: calcd. for $C_{35}H_{37}N_2O_{10}$ $[M-H]^-$ 645.2448, found 645.2450.

1′-(*tert*-butyl)2-ethyl(1*S*,2*R*,3*R*,4*R*,5*S*,6*R*)-4-hydroxy-3-(2-hydroxy-5-methylbenzyl)-5-nitro-2′-oxo-6-phenylspiro[cyclohexane-1,3′-indoline]-1′,2-dicarboxylate (5v): 77% yield; $[\alpha]_D^{25}$ = +71.8 (*c* = 1.0 in $CHCl_3$); 99% ee, determined by chiral HPLC analysis [Daicel Chiralcel IC, *n*-hexane/*i*-PrOH = 85/15, 1.0 mL/min, λ = 201 nm, t_{major} = 4.77 min, t_{minor} = 8.59 min]; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.47 (d, *J* = 7.2 Hz, 1H), 7.41 (d, *J* = 7.7 Hz, 1H), 7.23–7.13 (m, 2H), 7.06–6.86 (m, 5H), 6.73 (d, *J* = 8.0 Hz, 1H), 6.10 (s, 1H), 6.03 (dd, *J* = 12.3, 2.2 Hz, 1H), 4.38 (s, 1H), 4.11 (d, *J* = 12.4 Hz, 2H), 3.91–3.84 (m, 2H), 3.64 (d, *J* = 11.9 Hz, 1H), 3.38–3.29 (m, 1H), 3.01 (t, *J* = 12.8 Hz, 1H), 2.40 (dd, *J* = 13.6, 4.2 Hz, 1H), 2.28 (s, 3H), 1.56 (s, 8H), 0.87 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 174.79, 171.30, 154.30, 148.41, 147.48, 139.40, 132.94, 129.04, 127.88, 127.55, 124.74, 124.35, 122.76, 116.69, 116.28, 114.77, 113.92, 85.89, 84.17, 68.24, 61.06, 55.83, 54.63, 51.00, 46.64, 39.45, 29.72, 28.04, 13.63. ESI-HRMS: calcd. for $C_{35}H_{37}N_2O_9$ $[M-H]^-$ 629.2499, found 629.2495.

di-*tert*-butyl(1*S*,2*R*,3*R*,4*R*,5*S*,6*R*)-4-hydroxy-3-(2-hydroxybenzyl)-5-nitro-2′-oxo-6-phenylspiro[cyclohexane-1,3′-indoline]-1′,2-dicarboxylate (5w): 73% yield; $[\alpha]_D^{25}$ = +48.8 (*c* = 1.0 in $CHCl_3$); 98% ee, determined by chiral HPLC analysis [Daicel Chiralcel IC, *n*-hexane/*i*-PrOH = 85/15, 1.0 mL/min, λ = 201 nm, t_{major} = 3.84 min, t_{minor} = 8.05 min]; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.49 (d, *J* = 7.2 Hz, 1H), 7.43 (d, *J* = 7.9 Hz, 1H), 7.24–7.12 (m, 4H), 7.04–6.91 (m, 4H), 6.86–6.80 (m, 2H), 6.03 (dd, *J* = 12.3, 2.5 Hz, 1H), 4.38 (s, 1H), 4.18–4.09 (m, 2H), 3.51 (d, *J* = 11.9 Hz, 1H), 3.35–3.27 (m, 1H), 3.04 (t, *J* = 12.8 Hz, 1H), 2.49 (dd, *J* = 13.7, 4.0 Hz, 1H), 1.55 (s, 9H), 1.11 (d, *J* = 8.4 Hz, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 174.65, 170.20, 153.86, 148.49, 139.42, 133.09, 131.72, 128.93, 128.29, 127.83, 127.72, 124.31, 124.01, 123.03, 121.53, 115.82, 114.65, 85.97, 84.06, 81.98, 68.16, 54.74, 51.92, 46.67, 39.50, 29.29, 28.04, 27.30. ESI-HRMS: calcd. for $C_{36}H_{39}N_2O_9$ $[M-H]^-$ 643.2656, found 643.2651.

1′-(*tert*-butyl)2-ethyl(1*S*,2*R*,3*R*,4*R*,5*S*,6*R*)-4-hydroxy-3-(2-((4-methylphenyl)sulfonamido)ethyl)-5-nitro-2′-oxo-6-phenylspiro[cyclohexane-1,3'-indoline]-1′,2-dicarboxylate (5x): 47% yield; $[\alpha]_D^{25}$ = +32.6 (*c* = 1.0 in $CHCl_3$); 93% ee, determined by chiral HPLC analysis [Daicel Chiralcel IC, *n*-hexane/*i*-PrOH = 85/15, 1.0 mL/min, λ = 201 nm, t_{major} = 11.21 min, t_{minor} = 8.98 min]; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.76 (d, *J* = 8.2 Hz, 2H), 7.43–7.40 (m, 1H), 7.38–7.30 (m, 3H), 7.19–7.11 (m, 2H), 7.07–6.92 (m, 3H), 6.07 (dd, *J* = 12.3, 2.2 Hz, 1H), 4.89 (t, *J* = 6.0 Hz, 1H), 4.58 (s, 1H), 4.05 (d, *J* = 12.3 Hz, 1H), 3.80–3.66 (m, 2H), 3.49 (d, *J* = 12.0 Hz, 1H), 3.29 (d, *J* = 3.0 Hz, 1H), 3.16 (t, *J* = 10.0 Hz, 1H), 3.10–2.97 (m, 2H), 2.43 (s, 3H), 1.97–1.81 (m, 1H), 1.55 (s, 8H), 0.76 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 174.76, 170.94, 148.31, 143.70, 139.27, 136.32, 132.56, 129.86, 129.04, 128.00, 127.89, 127.28, 127.18, 124.33, 122.83, 114.73, 86.40, 84.19, 68.15, 61.04, 54.40, 50.49, 46.67, 40.41, 35.37, 29.04, 28.04, 21.53, 13.46. ESI-HRMS: calcd. for $C_{36}H_40N_3O_{10}S$ $[M-H]^-$ 706.2434, found 706.2437.

3.3. One-Pot, Three-Component Tandem Reaction to Access Spirocyclic Oxindole

To a mixture of **3** (0.02 mmol, 0.2 equiv) and *p*-nitrobenzoic acid (0.02 mmol, 0.2 equiv) in acetonitrile (0.2 mL) was added olefinic oxindole **1a** (0.1 mmol, 1 equiv), lactol **2a** (0.12 mmol, 1.2 equiv) and α,β-unsaturated aldehyde **6** (0.12 mmol, 1.2 equiv) in one portion. The reaction was stirred at 25 °C for 24 h. After completion, the mixture was directly subjected to column chromatography using (EtOAc/petroleum ether = 1:5) as eluent to give the product **7** for NMR and chiral HPLC analysis.

(**7**): 57% yield; $[\alpha]_D^{25} = -61.1$ ($c = 1.0$ in $CHCl_3$); 99% ee, determined by chiral HPLC analysis [Daicel Chiralcel IC, *n*-hexane/*i*-PrOH = 85/15, 1.0 mL/min, λ = 201 nm, t_{major} = 13.04 min, t_{minor} = 9.19 min]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.40 (s, 1H), 7.79 (d, J = 8.2 Hz, 1H), 7.43 (d, J = 2.0 Hz, 1H), 7.29 (dd, J = 7.5, 1.3 Hz, 1H), 7.24–7.16 (m, 3H), 6.98–6.92 (m, 2H), 6.80 (t, J = 11.6 Hz, 2H), 6.74–6.70 (m, 1H), 6.33 (d, J = 6.0 Hz, 1H), 5.70 (d, J = 5.9 Hz, 1H), 5.50 (d, J = 7.1 Hz, 1H), 3.89–3.75 (m, 4H), 3.34 (dd, J = 14.2, 4.2 Hz, 1H), 3.10 (d, J = 10.9 Hz, 1H), 2.95 (dd, J = 14.2, 5.6 Hz, 1H), 1.64 (s, 8H), 0.82 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.49, 174.58, 172.21, 155.12, 154.63, 149.30, 139.39, 138.13, 135.73, 133.40, 132.45, 128.86, 128.78, 126.75, 125.24, 123.19, 122.52, 120.50, 116.79, 114.40, 84.53, 61.81, 50.55, 46.75, 44.08, 38.47, 31.59, 28.12, 13.21. ESI-HRMS: calcd. for $C_{35}H_{35}ClNO_7$ $[M + H]^+$ 616.2102, found 616.2104.

4. Conclusions

In summary, we have reported a one-pot organo/organo dual catalytic system-induced [2+2+2] tandem reaction for the asymmetric synthesis of six-membered carbocycles with excellent enantioselectivities as a single diastereoisomer. The process enables the formation of a series of spiro oxindolic carbocyclic derivatives with versatile molecular complexity, which might have potential bioactivity. We believe that this asymmetric organo/organo dual catalytic system-induced one-pot strategy may enable further application of lactol or cyclic hemiaminal in the synthesis of structural diversification of carbocycles and heterocycles. Additional results will be reported in due course.

Supplementary Materials: The supplementary materials are available online at www.mdpi.com/2073-4344/6/5/65/s1.

Acknowledgments: We thank the National Nature Science Foundation of China (NO. 21302156, 81473337, 81274184), NSFC-Shandong Joint Fund for Marine Science Research Centers (NO. U1406402), Opening subject of state key laboratory of pharmaceutical biotechnology (KF-GN-201404) and Ocean University of China (OUC) for generous financial support.

Author Contributions: Zhi-Long Li and Yan-Kai Liu conceived and designed the experiments. Zhi-Long Li and Chao Liu performed the experiments and analyzed the data. Zhi-Long Li, Rui Tan, Zhi-Ping Tong and Yan-Kai Liu wrote the paper.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Chauhan, P.; Mahajan, S.; Kaya, U.; Hack, D.; Enders, D. Bifunctional amine-squaramides: Powerful hydrogen-bonding organocatalysts for asymmetric domino/cascade reactions. *Adv. Synth. Catal.* **2015**, *357*, 253–281. [CrossRef]
2. Volla, C.M.R.; Atodiresei, I.; Reuping, M. Catalytic C–C bond-forming multi-component cascade or domino reactions: Pushing the boundaries of complexity in asymmetric organocatalysis. *Chem. Rev.* **2014**, *114*, 2390–2431. [CrossRef] [PubMed]
3. Cioc, R.C.; Ruijter, E.; Orru, R.V.A. Multicomponent reactions: Advanced tools for sustainable organic synthesis. *Green Chem.* **2014**, *16*, 2958–2975. [CrossRef]
4. Pellissier, H. Recent developments in asymmetric organocatalytic domino reactions. *Adv. Synth. Catal.* **2012**, *354*, 237–294. [CrossRef]
5. Albrecht, Ł.; Jiang, H.; Jørgensen, K.A. A simple recipe for sophisticated cocktails: Organocatalytic one-pot reactions—Concept, nomenclature, and future perspectives. *Angew. Chem. Int. Ed.* **2011**, *50*, 8492–8509. [CrossRef] [PubMed]
6. Shao, Z.; Zhang, H. Combining transition metal catalysis and organocatalysis: A broad new concept for catalysis. *Chem. Soc. Rev.* **2009**, *38*, 2745–2755. [CrossRef] [PubMed]
7. Zhong, C.; Shi, X. When organocatalysis meets transition-metal catalysis. *Eur. J. Org. Chem.* **2010**, 2999–3025. [CrossRef]
8. Loh, C.C.J.; Enders, D. Merging organocatalysis and gold catalysis—A critical evaluation of the underlying concepts. *Chem. Eur. J.* **2012**, *18*, 10212–10225. [CrossRef] [PubMed]
9. Du, Z.; Shao, Z. Combining transition metal catalysis and organocatalysis—An update. *Chem. Soc. Rev.* **2013**, *42*, 1337–1378. [CrossRef] [PubMed]

10. Ding, Q.; Wu, J. Lewis acid- and organocatalyst-cocatalyzed multicomponent reactions of 2-alkynylbenzaldehydes, amines, and ketones. *Org. Lett.* **2007**, *9*, 4959–4962. [CrossRef] [PubMed]
11. Arróniz, C.; Gil-González, A.; Semak, V.; Escolano, C.; Bosch, J.; Amat, M. Cooperative catalysis for the first asymmetric formal [3+2] cycloaddition reaction of isocyanoacetates to α,β-unsaturated ketones. *Eur. J. Org. Chem.* **2011**, *2011*, 3755–3760. [CrossRef]
12. Zhang, Q.-W.; Xiang, K.; Tu, Y.-Q.; Zhang, S.-Y.; Zhang, X.-M.; Zhao, Y.-M.; Zhang, T.-C. Formal synthesis of (−)-cephalotaxine based on a tandem hydroamination/semipinacol rearrangement reaction. *Chem. Asian J.* **2012**, *7*, 894–898. [CrossRef] [PubMed]
13. Ortín, I.; Dixon, D.J. Direct catalytic enantio- and diastereoselective Mannich reaction of isocyanoacetates and ketimines. *Angew. Chem. Int. Ed.* **2014**, *53*, 3462–3465. [CrossRef] [PubMed]
14. Chi, Y.; Scroggins, S.T.; Fréchet, J.M.J. One-pot multi-component asymmetric cascade reactions catalyzed by soluble star polymers with highly branched non-interpenetrating catalytic cores. *J. Am. Chem. Soc.* **2008**, *130*, 6322–6323. [CrossRef] [PubMed]
15. Lathrop, S.P.; Rovis, T. Asymmetric synthesis of functionalized cyclopentanones via a multicatalytic secondary amine/N-heterocyclic carbene catalyzed cascade sequence. *J. Am. Chem. Soc.* **2009**, *131*, 13628–13630. [CrossRef] [PubMed]
16. Jiang, H.; Elsner, P.; Jensen, K.L.; Falcicchio, A.; Marcos, V.; Jørgensen, K.A. Achieving molecular complexity by organocatalytic one-pot strategies—A fast entry for synthesis of sphingoids, amino sugars, and polyhydroxylated α-Amino acids. *Angew. Chem. Int. Ed.* **2009**, *48*, 6844–6848. [CrossRef] [PubMed]
17. Wang, Y.; Han, R.-G.; Zhao, Y.-L.; Yang, S.; Xu, P.-F.; Dixon, D.J. Asymmetric organocatalytic relay cascades: Catalyst-controlled stereoisomer selection in the synthesis of functionalized cyclohexanes. *Angew. Chem. Int. Ed.* **2009**, *48*, 9834–9838. [CrossRef] [PubMed]
18. Pihko, P.M.; Rahaman, H.; Madarász, Á.; Pápai, I. Dual hydrogen-bond/enamine catalysis enables a direct enantioselective three-component domino reaction. *Angew. Chem. Int. Ed.* **2011**, *50*, 6123–6127.
19. Talavera, G.; Reyes, E.; Vicario, J.L.; Carrillo, L. Cooperative dienamine/hydrogen-bonding catalysis: Enantioselective formal [2+2] cycloaddition of enals with nitroalkenes. *Angew. Chem. Int. Ed.* **2012**, *51*, 4104–4107. [CrossRef] [PubMed]
20. Parra, A.; Reboredo, S.; Alemán, J. Asymmetric synthesis of cyclobutanes by a formal [2+2] cycloaddition controlled by dienamine catalysis. *Angew. Chem. Int. Ed.* **2012**, *51*, 9734–9736. [CrossRef] [PubMed]
21. Dewick, P.M. *Medicinal Natural Products. A Biosynthetic Approach*, 2nd ed.; Wiley: Chichester, UK, 2002.
22. Hale, K.J. Terpenoid- and shikimate-derived natural product total synthesis: A personal analysis and commentary on the importance of the papers that appear in this virtual issue. *Org. Lett.* **2013**, *15*, 3181–3198. [CrossRef] [PubMed]
23. Goudedranche, S.; Raimondi, W.; Bugaut, X.; Constantieux, T.; Bonne, D. Enantioselective organocatalyzed domino synthesis of six-membered carbocycles. *Synthesis* **2013**, *45*, 1909–1930.
24. Grondal, C.; Jeanty, M.; Enders, D. Organocatalytic cascade reactions as a new tool in total synthesis. *Nat. Chem.* **2010**, *2*, 167–178. [CrossRef] [PubMed]
25. Carlone, A.; Marigo, M.; North, C.; Landa, A.; Jørgensen, K.A. A simple asymmetric organocatalytic approach to optically active cyclohexenones. *Chem. Commun.* **2006**, *38*, 4928–4930. [CrossRef] [PubMed]
26. Duce, S.; Jorge, M.; Alonso, I.; Ruano, J.L.G.; Cid, M.B. An organocatalytic approach to enantiomerically enriched a-arylcyclohexenones and cyclohexanones. *Org. Biomol. Chem.* **2011**, *9*, 8253–8260. [CrossRef] [PubMed]
27. Albert, M.; Ramon, R. Asymmetric organocatalytic cyclization and cycloaddition reactions. *Chem. Rev.* **2011**, *111*, 4703–4832.
28. Zhou, F.; Liu, Y.-L.; Zhou, J. Catalytic asymmetric synthesis of oxindoles bearing a tetrasubstituted stereocenter at the C-3 position. *Adv. Synth. Catal.* **2010**, *352*, 1381–1407. [CrossRef]
29. Galliford, C.V.; Scheidt, K.A. Pyrrolidinyl-spirooxindole natural products as inspirations for the development of potential therapeutic agents. *Angew. Chem. Int. Ed.* **2007**, *46*, 8748–8758. [CrossRef] [PubMed]
30. Dalpozzo, R.; Bartoli, G.; Bencivenni, G. Recent advances in organocatalytic methods for the synthesis of disubstituted 2- and 3-indolinones. *Chem. Soc. Rev.* **2012**, *41*, 7247–7290. [CrossRef] [PubMed]
31. Venkatesan, H.; Davis, M.C.; Altas, Y.; Snyder, J.P.; Liotta, D.C. Total synthesis of SR 121463 A, a highly potent and selective vasopressin V2 receptor antagonist. *J. Org. Chem.* **2001**, *66*, 3653–3661. [CrossRef] [PubMed]

32. Tan, B.; Hernandez-Torres, G.; Barbas, C.F., III. Highly efficient hydrogen-bonding catalysis of the Diels–Alder reaction of 3-vinylindoles and methyleneindolinones provides carbazolespirooxindole skeletons. *J. Am. Chem. Soc.* **2011**, *133*, 12354–12357. [CrossRef] [PubMed]
33. Bencivenni, G.; Wu, L.-Y.; Mazzanti, A.; Giannichi, B.; Pesciaioli, F.; Song, M.-P.; Bartoli, G.; Melchiorre, P. Targeting structural and stereochemical complexity by organocascade catalysis: Construction of spirocyclic oxindoles having multiple stereocenters. *Angew. Chem. Int. Ed.* **2009**, *48*, 7200–7203. [CrossRef] [PubMed]
34. Jiang, K.; Jia, Z.-J.; Yin, X.; Wu, L.; Chen, Y.-C. Asymmetric quadruple aminocatalytic domino reactions to fused carbocycles incorporating a spirooxindole motif. *Org. Lett.* **2010**, *12*, 2766–2769. [CrossRef] [PubMed]
35. Wei, Q.; Gong, L.-Z. Organocatalytic asymmetric formal [4+2] cycloaddition for the synthesis of spiro[4-cyclohexanone-1,3′-oxindoline] derivatives in high optical purity. *Org. Lett.* **2010**, *12*, 1008–1011. [CrossRef] [PubMed]
36. Miller, K.A.; Tsukamoto, S. Rapid access to spirocyclic oxindoles: Application of asymmetric N-heterocyclic carbene-catalyzed [3+3] cycloaddition of imines to oxindole-derived enals. *Org. Lett.* **2015**, *17*, 2318–2321.
37. Moyano, A.; Companyó, X. Chapter 4—Catalytic asymmetric strategies for the synthesis of 3,3-disubstituted oxindoles. *Stud. Nat. Prod. Chem.* **2013**, *40*, 71–132.
38. Jiang, K.; Jia, Z.-J.; Chen, S.; Wu, L.; Chen, Y.-C. Organocatalytic tandem reaction to construct six-membered spirocyclic oxindoles with multiple chiral centres through a formal [2+2+2] Annulation. *Chem. Eur. J.* **2010**, *16*, 2852–2856. [CrossRef] [PubMed]
39. Companyó, X.; Zea, A.; Alba, A.R.; Mazzanti, A.; Moyano, A.; Rios, R. Organocatalytic synthesis of spiro compounds via a cascade Michael–Michael–aldol reaction. *Chem. Commun.* **2010**, *46*, 6953–6955. [CrossRef] [PubMed]
40. Chatterjee, I.; Bastida, D.; Melchiorre, P. Vinylogous organocatalytic triple cascade reaction: Forging six stereocenters in complex spiro-oxindolic cyclohexanes. *Adv. Synth. Catal.* **2013**, *355*, 3124–3130. [CrossRef]
41. Liu, Y.-K.; Li, Z.-L.; Li, J.-Y.; Feng, H.-X.; Tong, Z.-P. Open-close: An alternative strategy to α-functionalization of lactone via enamine catalysis in one pot under mild conditions. *Org. Lett.* **2015**, *17*, 2022–2025. [CrossRef] [PubMed]
42. Feng, H.-X.; Tan, R.; Liu, Y.-K. An efficient one-pot approach to the construction of chiral nitrogen-containing heterocycles under mild conditions. *Org. Lett.* **2015**, *17*, 3794–3797. [CrossRef] [PubMed]
43. Li, J.-Y.; Li, Z.-L.; Zhao, W.-W.; Liu, Y.-K.; Tong, Z.-P.; Tan, R. One-pot, highly efficient, asymmetric synthesis of ring-fused piperidine derivatives bearing *N*,*O*- or *N*,*N*-acetal moieties. *Org. Biomol. Chem.* **2016**, *14*, 2444–2453. [CrossRef] [PubMed]
44. Sun, X.-L.; Chen, Y.-H.; Zhu, D.-Y.; Zhang, Y.; Liu, Y.-K. Substrate-controlled, one-pot synthesis: Access to chiral chroman-2-one and polycyclic derivatives. *Org. Lett.* **2016**, *18*, 864–867. [CrossRef] [PubMed]
45. Zhu, Y.; Qian, P.; Yang, J.; Chen, S.; Hu, Y.; Wu, P.; Wang, W.; Zhang, W.; Zhang, S. Organocatalytic enantioselective Michael addition of cyclic hemiacetals to nitroolefins: A facile access to chiral substituted 5- and 6-membered cyclic ethers. *Org. Biomol. Chem.* **2015**, *13*, 4769–4775. [CrossRef] [PubMed]
46. Wang, J.; Qian, P.; Hua, Y.; Yang, J.; Jiang, J.; Chen, S.; Zhang, Y.; Zhang, S. Organocatalytic aldol addition reaction of cyclic hemiacetals to aldehydes. *Tetrahedron Lett.* **2015**, *56*, 2875–2877. [CrossRef]
47. CCDC 1468094 Contains The Supplementary Crystallographic Data of Racemate **5g**. Available online: www.ccdc.cam.ac.uk/data_request/cif (accessed on 15 March 2016).