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Gold(I)-catalyzed rearrangement of alkynylaziridine indoles for the synthesis of spiro-tetrahydro-β-carbolines☆

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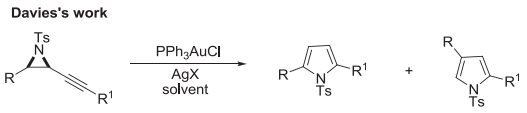
ABSTRACT

Functionalized spiro-tetrahydro-β-carbolines were formed by an efficient gold(I)-catalyzed rearrangement reaction of alkynylaziridine indoles. The reaction involved a Friedel–Crafts type intramolecular reaction of alkynylaziridine indoles, following by hydroamination of aminoallene intermediate.

1. Introduction

Tetrahydro-β-carbolines (THBCs), both naturally occurring and synthetic ones, are highly important alkaloids with valuable biological activities and pharmaceutical applications.[1] The syntheses of structural diversities and the complexity of pharmacologically active THBC derivatives result in a great synthetic challenge. Pictet–Spengler reactions have a large impact on preparing diverse THBCs over the past century.[2] In recent years, various asymmetric catalytic examples have been developed.[3] To date, only a handful of examples for the synthesis of spiro-THBCs has been reported, especially for the 4-substituted spiro-THBCs.[4] Therefore, development of effective methods for the synthesis of 4-spiro-THBC derivatives is desirable and challenging.

In the past decade, cationic gold(I) and silver(I) complexes, both π and σ Lewis acidities, have gained increasing interest due to their reaction mildness and efficiency.[5,6] Because aziridine building block is so useful for the synthesis of nitrogen-containing biologically active molecules, the number of gold-catalyzed transformation of aziridines has increased rapidly.[7–9] In 2009, Davies introduced a gold-catalyzed ring-expansion and rearrangement of aryl-substituted *N*-tosyl alkynyl aziridines to di-substituted pyrrole products [Scheme 1].[7] In 2010, Pale reported a gold-catalyzed tandem rearrangement-nucleophilic substitution of acetoxylated alkynyl oxiranes and aziridines to form furans and pyrroles in the presence of nucleophiles [Scheme 2, Eq. 1].[8] Recently, the investigations developed by Pale and co-workers were carried out, alkynyl aziridines with aryl group could be efficiently converted to spiro[isochroman-4,2′-pyrrolines] using gold catalysts [Scheme 2, Eq. 2].[9] In continuation of our studies on spriocyclic compounds,[10] we report herein the synthesis of spiro-tetrahydro-β-carbolines **2** from the C2-alkynylaziridine indoles **1** using gold(I) catalysis via a Friedel–Crafts type intramolecular reaction[11] followed by hydroamination of allenes[12] [Scheme 2, Eq. 3]. In this reaction, two rings with a spirocarbon can be efficiently formed.



Scheme 1. Gold-catalyzed ring-expansion and rearrangement reaction.

2. Results and discussion

To examine our hypotheses, we chose alkynylaziridine indole **1a** as a model substrate, which was synthesized by the Mitsunobu

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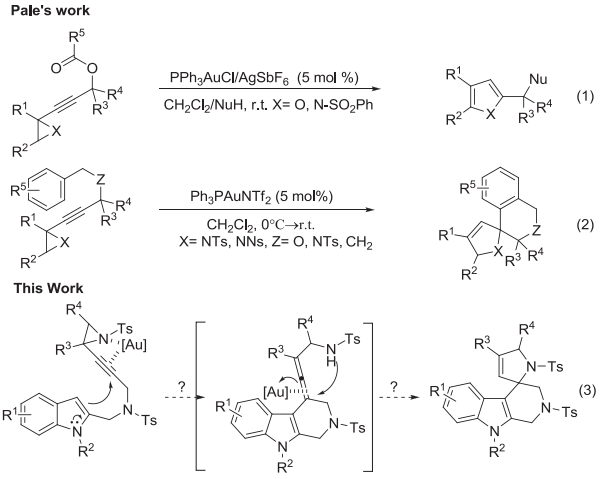
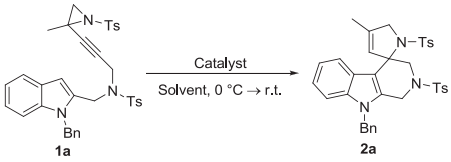


Scheme 2. Previous works and present work.

reaction of *N*-substituted-4-dimethylbenzenesulfonamide and aziridine propargylic alcohol. First, several gold(III) catalysts were studied. Regretfully, it was detrimental to generate the spiro-THBCs when the catalyst was trivalent gold (Table 1, entries 1–3). Then, studies of gold(I) catalysts were carried out. Delightedly, spiro-THBC **2a** was isolated with 56% yield when PPh_3AuNTf_2 was used (entry 4). The relative configuration of product **2a** was determined by X-ray diffraction (Fig. 1).[13] Other gold(I) catalysts, such as $[Au(PPh_3)(MeCN)]SbF_6$ and $[Au(JohnPhos)(MeCN)]SbF_6$ could also catalyze the reaction, giving moderate yields (entries 5 and 6). When we used AuI or $Au(PPh_3)Cl$ as catalysts, no reaction occurred (entries 7 and 8). Experiments using $Au(PPh_3)Cl$ in combination with $AgSbF_6$, AgOTf, and $AgBF_4$ were also carried out (entries 9–11). It showed that 5 mol % of $Au(PPh_3)Cl/AgSbF_6$ was the most efficient, with the expected product **2a** in 84% yield (entry 9). The reaction

Table 1
Optimization of reaction conditions[a]



Entry	Catalyst (5 mol %)	Solvent	Time (h)	Yield[b] (%)
1	$AuCl_3$	DCM	12	NR
2	$NaAuCl_4·2H_2O$	DCM	12	NR
3	$HAuCl_4·3H_2O$	DCM	12	NR
4	PPh_3AuNTf_2	DCM	5	56
5	$[Au(PPh_3)(MeCN)]SbF_6$	DCM	5	68
6[c]	$[Au(JohnPhos)(MeCN)]SbF_6$	DCM	5	68
7	AuI	DCM	12	NR
8	$Au(PPh_3)Cl$	DCM	12	NR
9	$Au(PPh_3)Cl$, $AgSbF_6$	DCM	5	84
10	$Au(PPh_3)Cl$, AgOTf	DCM	5	74
11	$Au(PPh_3)Cl$, $AgBF_4$	DCM	5	81
12	$AgNTf_2$	DCM	5	65
13	$AgSbF_6$	DCM	5	74
14	AgOTf	DCM	5	61
15	$AgBF_4$	DCM	5	51
16	$Au(PPh_3)Cl$, $AgSbF_6$	DCE	5	77
17	$Au(PPh_3)Cl$, $AgSbF_6$	1,4-Dioxane	5	70
18	$Au(PPh_3)Cl$, $AgSbF_6$	CH_3NO_2	5	76
19	$Au(PPh_3)Cl$, $AgSbF_6$	THF	5	68

[a] The reaction was conducted by using **1a** (0.1 mmol), catalyst (5 mol %) in solvent (3 mL) at 0 °C to room temperature.
[b] Isolated yield.
[c] JohnPhos=(2-biphenyl)di-*tert*-butylphosphine.

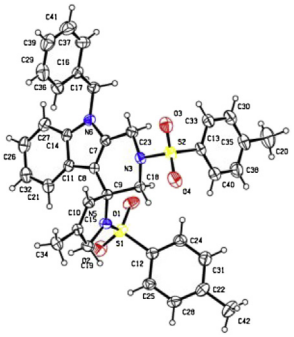
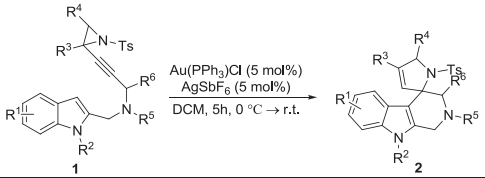


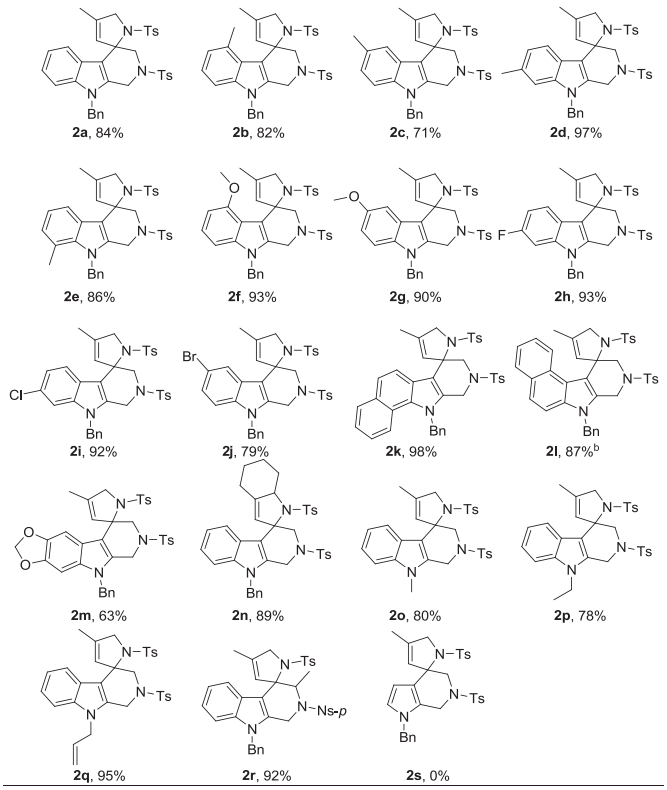
Fig. 1. X-ray crystal structure of **2a**.

catalyzed by silver catalysts afforded 51–74% yields (entries 12–15). Further examination of solvent effects revealed that the use of 1,2-dichloroethane (DCE), 1,4-dioxane, CH_3NO_2 or tetrahydrofuran (THF) decreased the yield (entries 16–19). After the systematic screening, the use of 5 mol % $Au(PPh_3)Cl$ and 5 mol % $AgSbF_6$ in dry dichloromethane at 0 °C to room temperature after 5 h were considered as the optimal reaction conditions.

Under the modified reaction conditions, we aimed to test the scope of the reaction and the results were shown in Table 2. The

Table 2
Gold(I)-Catalyzed synthesis of various tetrahydro-β-carbolines[a]

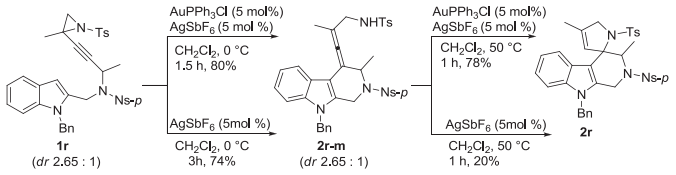




[a] The reaction was carried out using **1** (0.1 mmol), $Au(PPh_3)Cl/AgSbF_6$ (5 mol%) in CH_2Cl_2 (3 mL) after 5h at 0 °C to room temperature. Isolated yield.
[b] The catalyst loading of $Au(PPh_3)Cl/AgSbF_6$ was 10 mol%.

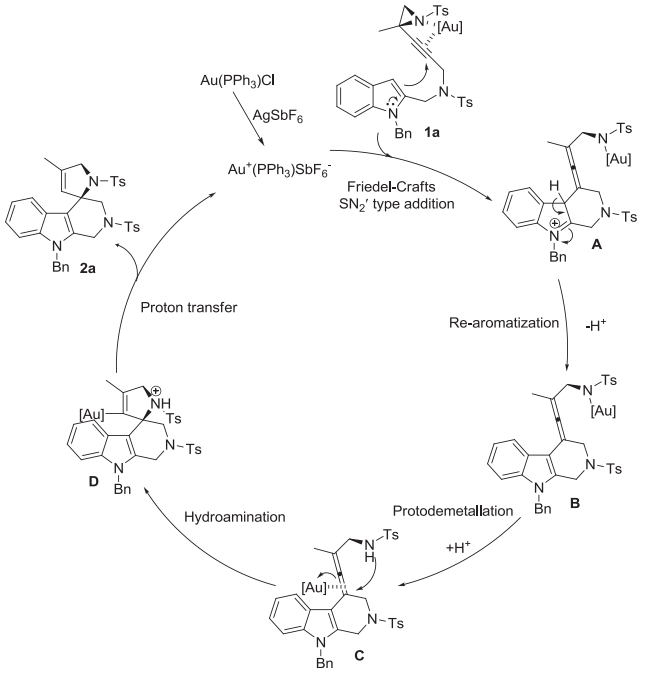
double cyclization of indoles bearing various substituents worked smoothly to give the corresponding spiro-THBC in moderate to good yields. For example, the reactions of the substituted indoles **1a**–**g** with methyl, methoxy groups furnished the spiro-THBCs **2a**–**g** in 71–97% yields and the substituted indoles **1h**–**j** with fluoro, chloro, bromo groups also reacted to give the products **2h**–**j** in 79–93% yields. This result showed that indoles containing electron-donating groups exhibited very similar reactivity in comparison to those bearing electron-withdrawing groups. When the substrate was alkynylaziridine benzo[*g*]indole, the reaction proceeded well, and the 7,8-benzosubstituted THBC **2k** was formed in 98% yield. Because of steric hindrance, complete conversion of alkynylaziridine benzo[*e*]indole **1l** could be observed when increasing in catalyst-loading up to 10 mol %, giving 5,6-benzosubstituted THBC **2l** in 87% yield. While 5,6-methylenedioxyindole derivative **1m** was conducted to the standard reaction conditions, **2m** was isolated in only 63% yield. Furthermore, trisubstituted aziridine, such as aziridine **1n** efficiently furnished the double-cyclization product **2n** in 89% yield. Changing the N-substitution R^2 group to methyl and ethyl have no obvious effect on the reaction, and we can easily get the corresponding products in good yields (**2o** and **2p**). Replacing benzyl with allyl, which offers a more stable protecting, increased slightly in the product yield (**2a** vs **2q**). When we replaced Ts with Ns-*p* (*p*-nitrobenzenesulfonyl), **1r** was easily prepared by Mitsunobu reaction.[14] For the methyl-substituented compound **1r** (dr=2.65:1), an excellent yield of 92% was isolated giving the corresponding spiro compound **2r**. When C2-alkynylaziridine pyrrole compound **1s** was used according to the standard reaction conditions, the reaction did not occur (**2s**).[15]

To get more insight into the mechanism, we studied the intermediate of different compounds. Delightedly, when methyl-substituented compound **1r** (dr=2.65:1) were conducted to 5 mol % $Au(PPh_3)Cl/AgSbF_6$ and 5 mol % $AgSbF_6$ in dry dichloromethane at 0 °C for 1.5 h and 3 h, intermediate **2r**–**m** were isolated in 80% and 74% yield (dr=2.65:1), respectively (Scheme 3). When intermediate **2r**–**m** were putted into the 5 mol % $Au(PPh_3)Cl/AgSbF_6$ and 5 mol % $AgSbF_6$ in dry dichloromethane at 50 °C for 1 h,[16] corresponding product **2r** were formed in 78% and 20%, respectively. Thus, the mechanism of silver-catalyzed is similar to the gold-catalyzed process. However, gold-catalyzed process is more efficient than silver-catalyzed process in the second step.



Scheme 3. Experimental confirmation of reaction mechanism.

A mechanism for this gold-catalyzed rearrangement reaction is proposed as shown in Scheme 4. Initially, alkynylaziridine moiety is activated by dual coordination of the gold(I) ion. An intramolecular nucleophilic addition of the indole (C3-position) to the activated alkynylaziridine, which concerted with an *anti*-opening of the aziridine part would lead to unstable cationic species intermediate **A**. It undergoes a re-aromatization step to give the allenyl indole **B**. The protodemetalation of intermediate **B** liberates α-aminoallene **C** and the metal ion. The latter could then activate the allene, promoting an *endo*-hydroamination cyclization,[12] affording vinyl gold intermediate **D**. Proton transfer of intermediate **D** would finally lead to the spiro-THBC **2a**.



Scheme 4. Mechanism for the gold(I)-catalyzed cascade reaction of alkynylaziridine indole.

3. Conclusions

In summary, we have presented an efficient method for the construction of spiro-THBCs. The approach uses a gold(I)-catalyzed tandem Friedel–Crafts type addition, followed by a cyclization reaction of the aminoallene intermediate. The very mild conditions, good functional group compatibility and operational simplicity are expected to make this reaction attractive to chemists. The application of this methodology to synthesize other members of the indole-containing motifs is currently under study in our laboratory.

4. Experimental section

4.1. General

Column chromatography was carried out on silica gel. Reagents and solvents were purified using standard means. ^1H NMR spectra were recorded on 400 MHz in $CDCl_3$ and ^{13}C NMR spectra were recorded on 100 MHz in $CDCl_3$ using TMS as internal standard. IR spectra were recorded on a FT-IR spectrometer and only major peaks are reported in cm^{-1}. Melting points were determined on a microscopic apparatus and were uncorrected. High-resolution mass spectral analysis (HRMS) data were recorded by Electro-Spray Ionization (ESI). The parent ions $[M+H]^+$, $[M+Na]^+$ or $[M+K]^+$ are quoted.

4.2. General procedure for the gold-catalyzed synthesis of spiro-tetrahydro-β-carbolines

To a dried tube, which wrapped in aluminum foil were added $Au(PPh_3)Cl$ (2.5 mg, 0.005 mmol), $AgSbF_6$ (1.7 mg, 0.005 mmol), and dry CH_2Cl_2 (1 mL) sequentially at room temperature. The resulting mixture was stirred at room temperature for about 0.5 h until it became purple, which was followed by the addition of **1** (0.1 mmol) and 2 mL of dry CH_2Cl_2 at 0 °C. The resulting mixture was allowed to warm at room temperature. Monitored by thin-layer chromatography, the reaction was stirred until complete conversion of the starting material. After concentration of the

reaction mixture, the crude residue was purified by flash chromatography on alkalescent silica gel (hexane/EtOAc=4/1) to afford **2**.

4.3. Characterization data of products

*4.3.1. 9-Benzyl-4′-methyl-1′,2-ditosyl-1,1′,2,3,5′,9-hexahydro-spiro[pyrido[3,4-b]indole-4,2′-pyrrole](**2a**).* Yellow solid; mp: 192–194 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, J=8.0 Hz, 2H), 7.35–7.26 (m, 5H), 7.10–7.04 (m, 5H), 6.97–6.93 (m, 1H), 6.66 (d, J=8.0 Hz, 2H), 6.58–6.54 (m, 1H), 6.44 (d, J=7.6 Hz, 1H), 5.56 (s, 1H), 5.27 (d, J_{ab}=16.8 Hz, 1H), 5.19 (d, J_{ab}=16.4 Hz, 1H), 4.67 (d, J=14.0 Hz, 1H), 4.39 (d, J_{ab}=13.2 Hz, 1H), 4.31 (d, J_{ab}=13.6 Hz, 1H), 3.97 (d, J_{ab}=11.6 Hz, 1H), 3.90 (d, J_{ab}=11.6 Hz, 1H), 3.82 (d, J=14.0 Hz, 1H), 2.44 (s, 3H), 2.19 (s, 3H), 1.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.0, 142.8, 136.8, 136.3, 135.7, 133.4, 131.9, 131.5, 130.0, 129.0, 128.5, 127.8, 127.5, 126.9, 126.1, 125.4, 121.1, 119.8, 118.7, 110.2, 109.3, 71.8, 58.7, 54.4, 47.0, 43.0, 21.6, 21.2, 14.0; IR (KBr, cm^{-1}) 2919, 1597, 1455, 1337, 1159, 750, 661; HRMS (ESI) m/z: calcd for $C_{36}H_{35}N_3O_4S_2$: M+H=638.2142; found: 638.2160.

*4.3.2. 9-Benzyl-4′,5-dimethyl-1′,2-ditosyl-1,1′,2,3,5′,9-hexahydro-spiro[pyrido[3,4-b]indole-4,2′-pyrrole] (**2b**).* Yellow solid; mp: 198–200 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, J=8.4 Hz, 2H), 7.34 (d, J=8.0 Hz, 2H), 7.29–7.23 (m, 5H), 7.00–6.94 (m, 6H), 6.63 (d, J=6.4 Hz, 1H), 5.76 (s, 1H), 5.22 (s, 2H), 4.55 (d, J=14.0 Hz, 1H), 4.28 (d, J_{ab}=13.2 Hz, 1H), 4.07 (d, J_{ab}=13.2 Hz, 1H), 3.84–3.72 (m, 3H), 2.46 (s, 3H), 2.34 (s, 3H), 2.08 (s, 3H), 1.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.1, 142.9, 137.3, 136.8, 136.6, 132.9, 132.6, 132.0, 131.2, 131.0, 129.9, 129.0, 128.8, 127.7, 127.6, 127.2, 125.9, 125.6, 122.4, 121.9, 111.2, 107.0, 73.3, 57.9, 55.7, 46.8, 43.5, 21.6, 21.4, 20.6, 14.2; IR (KBr, cm^{-1}) 2918, 1727, 1451, 1344, 1160, 753, 665; HRMS (ESI) m/z: calcd for $C_{37}H_{37}N_3O_4S_2$: M+Na=674.2118; found: 674.2134.

*4.3.3. 9-Benzyl-4′,6-dimethyl-1′,2-ditosyl-1,1′,2,3,5′,9-hexahydro-spiro[pyrido[3,4-b]indole-4,2′-pyrrole] (**2c**).* Yellow solid; mp: 194–196 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, J=8.4 Hz, 2H), 7.36–7.28 (m, 5H), 7.07 (d, J=6.8 Hz, 2H), 6.99–6.94 (m, 3H), 6.74–6.72 (m, 1H), 6.61 (d, J=8.0 Hz, 2H), 5.98 (s, 1H), 5.55 (s, 1H), 5.25 (d, J_{ab}=16.8 Hz, 1H), 5.17 (d, J_{ab}=16.8 Hz, 1H), 4.67 (d, J=14.0 Hz, 1H), 4.45 (d, J=13.6 Hz, 1H), 4.29 (d, J=13.6 Hz, 1H), 4.00–3.89 (m, 2H), 3.80 (d, J=14.0 Hz, 1H), 2.44 (s, 3H), 2.16 (s, 3H), 2.01 (s, 3H), 1.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.0, 142.4, 136.9, 135.5, 134.6, 133.4, 132.1, 131.3, 130.0, 129.0, 128.4, 128.2, 127.7, 127.6, 126.8, 126.0, 125.7, 122.7, 118.4, 109.4, 109.0, 71.8, 58.8, 54.6, 47.0, 43.0, 21.5, 21.1, 14.0; IR (KBr, cm^{-1}) 2918, 1596, 1449, 1338, 1159, 752, 662; HRMS (ESI) m/z: calcd for $C_{37}H_{37}N_3O_4S_2$: M+Na=674.2118; found: 674.2136.

*4.3.4. 9-Benzyl-4′,7-dimethyl-1′,2-ditosyl-1,1′,2,3,5′,9-hexahydro-spiro[pyrido[3,4-b]indole-4,2′-pyrrole] (**2d**).* Yellow solid; mp: 193–194 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, J=8.4 Hz, 2H), 7.35–7.28 (m, 5H), 7.06 (d, J=8.0 Hz, 4H), 6.89 (s, 1H), 6.69 (d, J=8.0 Hz, 2H), 6.40 (d, J_{ab}=8.0 Hz, 1H), 6.32 (d, J_{ab}=8.0 Hz, 1H), 5.54 (s, 1H), 5.24 (d, J_{ab}=16.8 Hz, 1H), 5.16 (d, J_{ab}=16.8 Hz, 1H), 4.63 (d, J=14.0 Hz, 1H), 4.39–4.29 (q, J=13.6 Hz, 2H), 3.95 (d, J_{ab}=11.6 Hz, 1H), 3.87 (d, J_{ab}=11.6 Hz, 1H), 3.78 (d, J=14.0 Hz, 1H), 2.44 (s, 3H), 2.32 (s, 3H), 2.21 (s, 3H), 1.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.0, 142.7, 136.9, 136.7, 135.8, 133.4, 131.3, 131.2, 131.1, 130.0, 129.0, 128.4, 127.7, 127.6, 127.5, 127.0, 126.0, 123.3, 121.6, 118.3, 110.2, 109.1, 71.8, 58.7, 54.3, 46.8, 42.9, 21.7, 21.6, 21.3, 13.9; IR (KBr, cm^{-1}) 2918, 1597, 1452, 1336, 1159, 754, 661; HRMS (ESI) m/z: calcd for $C_{37}H_{37}N_3O_4S_2$: M+Na=674.2118; found: 674.2134.

*4.3.5. 9-Benzyl-4′,8-dimethyl-1′,2-ditosyl-1,1′,2,3,5′,9-hexahydro-spiro[pyrido[3,4-b]indole-4,2′-pyrrole] (**2e**).* White solid; mp: 192–194 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, J=8.0 Hz, 2H), 7.33–7.25 (m, 5H), 7.15 (d, J=8.0 Hz, 2H), 6.89 (d, J=7.2 Hz, 2H), 6.81 (d, J=7.6 Hz, 2H), 6.70 (d, J=7.2 Hz, 1H), 6.50 (t, J=7.6 Hz, 1H), 6.42 (d, J=8.0 Hz, 1H), 5.56 (s, 1H), 5.48 (d, J_{ab}=18.0 Hz, 1H), 5.41 (d, J_{ab}=18.0 Hz, 1H), 4.62 (d, J=14.4 Hz, 1H), 4.35 (d, J_{ab}=13.2 Hz, 1H), 4.29 (d, J_{ab}=13.6 Hz, 1H), 3.95 (d, J_{ab}=11.2 Hz, 1H), 3.86 (d, J_{ab}=11.6 Hz, 1H), 3.81 (d, J=14.0 Hz, 1H), 2.45 (s, 3H), 2.43 (s, 3H), 2.26 (s, 3H), 1.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.0, 142.8, 138.5, 136.1, 135.2, 133.5, 132.3, 131.5, 129.9, 129.1, 128.6, 127.6, 127.5, 127.0, 126.1, 125.0, 124.5, 120.6, 120.0, 117.0, 110.8, 72.0, 58.6, 54.3, 48.6, 42.9, 21.5, 21.3, 19.6, 14.0; IR (KBr, cm^{-1}) 2918, 1599, 1449, 1336, 1159, 750, 663; HRMS (ESI) m/z: calcd for $C_{37}H_{37}N_3O_4S_2$: M+Na=674.2118; found: 674.2132.

*4.3.6. 9-Benzyl-5-methoxy-4′-methyl-1′,2-ditosyl-1,1′,2,3,5′,9-hexahydrospiro[pyrido[3,4-b]indole-4,2′-pyrrole] (**2f**).* Yellow solid; mp: 184–186 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, J=8.0 Hz, 2H), 7.34–7.28 (m, 5H), 7.05 (d, J=7.2 Hz, 2H), 7.00 (d, J=8.4 Hz, 2H), 6.87 (t, J=8.0 Hz, 1H), 6.71 (d, J=8.0 Hz, 1H), 6.65 (d, J=8.0 Hz, 2H), 5.90 (d, J=7.6 Hz, 1H), 5.62 (s, 1H), 5.23 (d, J_{ab}=16.8 Hz, 1H), 5.17 (d, J_{ab}=16.8 Hz, 1H), 4.62 (d, J=14.0 Hz, 1H), 4.33 (d, J_{ab}=12.4 Hz, 1H), 4.20 (d, J_{ab}=12.4 Hz, 1H), 3.97 (d, J_{ab}=11.6 Hz, 1H), 3.87 (d, J_{ab}=11.6 Hz, 1H), 3.76 (d, J=14.0 Hz, 1H), 3.27 (s, 3H), 2.43 (s, 3H), 2.18 (s, 3H), 1.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.7, 143.9, 142.0, 138.2, 136.9, 133.4, 132.0, 131.2, 130.0, 129.0, 128.7, 127.8, 127.7, 127.0, 126.0, 122.4, 116.6, 110.0, 102.5, 100.1, 72.6, 59.1, 56.0, 54.6, 47.1, 43.3, 21.5, 21.2, 14.2; IR (KBr, cm^{-1}) 2920, 1637, 1444, 1326, 1157, 1031; HRMS (ESI) m/z: calcd for $C_{37}H_{37}N_3O_5S_2$: M+Na=690.2067; found: 690.2079.

*4.3.7. 9-Benzyl-6-methoxy-4′-methyl-1′,2-ditosyl-1,1′,2,3,5′,9-hexahydrospiro[pyrido[3,4-b]indole-4,2′-pyrrole] (**2g**).* Yellow solid; mp: 164–166 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, J=8.0 Hz, 2H), 7.35–7.28 (m, 5H), 7.08 (d, J=6.8 Hz, 2H), 7.00 (d, J=8.4 Hz, 2H), 6.96 (d, J=8.8 Hz, 1H), 6.63–6.57 (m, 3H), 5.73 (d, J=2.0 Hz, 1H), 5.56 (s, 1H), 5.23 (d, J_{ab}=16.8 Hz, 1H), 5.16 (d, J_{ab}=16.4 Hz, 1H), 4.67 (d, J=14.0 Hz, 1H), 4.44 (d, J_{ab}=13.2 Hz, 1H), 4.26 (d, J_{ab}=13.6 Hz, 1H), 3.99 (d, J_{ab}=11.6 Hz, 1H), 3.91 (d, J_{ab}=11.6 Hz, 1H), 3.82 (d, J=14.4 Hz, 1H), 3.49 (s, 3H), 2.44 (s, 3H), 2.18 (s, 3H), 1.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.5, 144.0, 142.8, 136.9, 135.4, 133.5, 132.8, 131.4, 131.3, 130.0, 129.0, 128.4, 127.8, 127.5, 126.9, 126.1, 110.7, 110.1, 109.5, 100.6, 71.9, 58.8, 54.8, 54.6, 47.2, 43.1, 21.6, 21.1, 15.3; IR (KBr, cm^{-1}) 2920, 1595, 1452, 1339, 1160, 754, 665; HRMS (ESI) m/z: calcd for $C_{37}H_{37}N_3O_5S_2$: M+Na=690.2067; found: 690.2083.

*4.3.8. 9-Benzyl-7-fluoro-4′-methyl-1′,2-ditosyl-1,1′,2,3,5′,9-hexa-hydrospiro[pyrido[3,4-b]indole-4,2′-pyrrole] (**2h**).* Yellow solid; mp: 188–190 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, J=8.0 Hz, 2H), 7.53–7.27 (m, 5H), 7.06 (d, J=7.2 Hz, 2H), 7.02 (d, J=8.4 Hz, 2H), 6.99–6.95 (m, 1H), 6.69–6.64 (m, 3H), 5.89 (dd, J=2.4 Hz, 9.6 Hz, 1H), 5.54 (s, 1H), 5.24 (d, J_{ab}=16.8 Hz, 1H), 5.17 (d, J_{ab}=16.8 Hz, 1H), 4.68 (d, J=14.0 Hz, 1H), 4.44 (d, J_{ab}=13.6 Hz, 1H), 4.30 (d, J_{ab}=13.6 Hz, 1H), 3.98 (d, J_{ab}=12.0 Hz, 1H), 3.91 (d, J_{ab}=12.0 Hz, 1H), 3.82 (d, J=14.0 Hz, 1H), 2.44 (s, 3H), 2.19 (s, 3H), 1.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.5 (d, J=110 Hz, CF), 136.5, 135.6, 134.0, 133.5, 132.7, 131.8, 130.0, 129.1, 128.5, 128.0, 127.5, 127.3, 126.7, 126.1, 126.0, 110.0 (d, J=9.0 Hz), 109.4 (d, J=27.0 Hz), 103.9 (d, J=24.0 Hz), 71.5, 58.8, 54.6, 47.3, 43.0, 21.5, 21.1, 13.9; IR (KBr, cm^{-1}) 2919, 1595, 1451, 1340, 1160, 754, 664; HRMS (ESI) m/z: calcd for $C_{36}H_{34}FN_3O_4S_2$: M+Na=678.1867; found: 678.1876.

*4.3.9. 9-Benzyl-7-chloro-4′-methyl-1′,2-ditosyl-1,1′,2,3,5′,9-hexa-hydrospiro[pyrido[3,4-b]indole-4,2′-pyrrole] (**2i**).* Yellow solid; mp: 202–204 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, J=8.4 Hz, 2H), 7.35–7.30 (m, 5H), 7.07 (d, J=8.0 Hz, 3H), 7.02 (d, J=8.0 Hz, 2H), 6.69 (d, J=8.0 Hz, 2H), 6.51 (dd, J=1.2, 8.4 Hz, 1H), 6.31 (d, J=8.4 Hz, 1H),

5.55 (s, 1H), 5.21 (d, J_{ab}=16.8 Hz, 1H), 5.15 (d, J_{ab}=16.8 Hz, 1H), 4.65 (d, J=14.4 Hz, 1H), 4.40 (d, J_{ab}=13.6 Hz, 1H), 4.29 (d, J_{ab}=13.2 Hz, 1H), 3.96 (d, J_{ab}=12.0 Hz, 1H), 3.89 (d, J_{ab}=12.0 Hz, 1H), 3.80 (d, J=14.0 Hz, 1H), 2.44 (s, 3H), 2.25 (s, 3H), 1.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.1, 143.3, 136.7, 136.2, 135.7, 133.5, 133.0, 131.8, 130.0, 129.1, 128.5, 128.0, 127.5, 127.4, 126.9, 126.1, 124.2, 120.5, 119.4, 110.5, 109.2, 71.5, 58.8, 54.3, 47.2, 42.9, 21.5, 21.2, 13.9; IR (KBr, cm^{-1}) 2919, 1598, 1451, 1335, 1159, 754, 662; HRMS (ESI) m/z: calcd for $C_{36}H_{34}ClN_3O_4S_2$: M+Na=694.1571; found: 694.1585.

*4.3.10. 9-Benzyl-6-bromo-4′-methyl-1′,2-ditosyl-1,1′,2,3,5′,9-hexahydrospiro[pyrido[3,4-b]indole-4,2′-pyrrole] (**2j**).* White solid; mp: 218–220 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, J=8.4 Hz, 2H), 7.35–7.30 (m, 5H), 7.07 (d, J=6.8 Hz, 2H), 7.00–6.92 (m, 4H), 6.66 (d, J=8.0 Hz, 2H), 6.26 (s, 1H), 5.53 (s, 1H), 5.24 (d, J_{ab}=16.8 Hz, 1H), 5.17 (d, J_{ab}=16.8 Hz, 1H), 4.68 (d, J=14.4 Hz, 1H), 4.47 (d, J_{ab}=13.6 Hz, 1H), 4.28 (d, J_{ab}=13.6 Hz, 1H), 3.99 (d, J_{ab}=12.0 Hz, 1H), 3.92 (d, J_{ab}=11.6 Hz, 1H), 3.81 (d, J=14.0 Hz, 1H), 2.44 (s, 3H), 2.21 (s, 3H), 1.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.1, 143.1, 136.3, 135.2, 134.8, 133.8, 133.4, 131.9, 130.0, 129.1, 128.6, 128.1, 127.5, 127.3, 127.1, 126.5, 126.1, 123.9, 121.3, 113.4, 110.8, 109.7, 71.4, 58.9, 54.6, 47.3, 42.9, 21.6, 21.3, 14.0; IR (KBr, cm^{-1}) 2918, 1598, 1455, 1159, 754, 663; $C_{36}H_{34}BrN_3O_4S_2$: M+Na=738.1066; found: 738.1071.

*4.3.11. 11-Benzyl-4′-methyl-1′,9-ditosyl-1′,5′,8,9,10,11-hexa-hydrospiro[benzo[g]pyrido[3,4-b]indole-7,2′-pyrrole] (**2k**).* Yellow solid; mp: 120–122 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99–7.97 (m, 1H), 7.77–7.74 (m, 1H), 7.70 (d, J=8.0 Hz, 2H), 7.36–7.28 (m, 7H), 7.13 (d, J=7.2 Hz, 2H), 7.05 (d, J=8.4 Hz, 2H), 6.94 (d, J=8.8 Hz, 1H), 6.57 (d, J=8.4 Hz, 1H), 6.50 (d, J=8.0 Hz, 2H), 5.75–5.60 (m, 3H), 4.75 (d, J=14.0 Hz, 1H), 4.46 (d, J_{ab}=13.6 Hz, 1H), 4.37 (d, J_{ab}=13.2 Hz, 1H), 4.04–3.93 (m, 3H), 2.43 (s, 3H), 1.97 (s, 3H), 1.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.0, 142.9, 136.7, 135.8, 133.7, 131.6, 131.4, 130.9, 130.0, 129.8, 129.3, 128.9, 128.4, 127.9, 127.8, 127.5, 127.0, 125.6, 125.4, 123.3, 123.0, 122.1, 121.5, 120.4, 118.0, 111.6, 71.9, 58.8, 54.6, 49.9, 43.0, 21.5, 21.0, 14.0; IR (KBr, cm^{-1}) 2919, 1598, 1447, 1349, 1160, 749, 664; HRMS (ESI) m/z: calcd for $C_{40}H_{37}N_3O_4S_2$: M+Na=710.2118; found: 710.2132.

*4.3.12. 7-Benzyl-4′-methyl-1′,9-ditosyl-1′,5′,7,8,9,10-hexahydro-spiro[benzo[e]pyrido[3,4-b]indole-11,2′-pyrrole] (**2l**).* Yellow solid; mp: 191–193 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, J=8.0 Hz, 2H), 7.66 (d, J=8.0 Hz, 1H), 7.44–7.24 (m, 8H), 7.15 (t, J=7.2 Hz, 1H), 7.02 (d, J=6.8 Hz, 2H), 6.95 (t, J=7.2 Hz, 1H), 6.72 (d, J=8.4 Hz, 2H), 6.21 (d, J=8.0 Hz, 2H), 5.86 (s, 1H), 5.39 (d, J_{ab}=16.8 Hz, 1H), 5.33 (d, J_{ab}=17.2 Hz, 1H), 4.70 (d, J=14.0 Hz, 1H), 4.64 (d, J_{ab}=14.0 Hz, 1H), 4.35 (d, J_{ab}=13.6 Hz, 1H), 4.06 (d, J_{ab}=11.6 Hz, 1H), 3.94 (d, J_{ab}=12.0 Hz, 1H), 3.90 (d, J=14.0 Hz, 1H), 2.44 (s, 3H), 1.95 (s, 3H), 1.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.1, 142.0, 136.5, 135.6, 133.4, 133.3, 131.2, 130.2, 130.0, 129.6, 129.1, 127.9, 127.8, 127.7, 127.5, 126.5, 125.9, 125.2, 124.7, 123.4, 122.6, 121.1, 112.3, 110.8, 73.2, 58.7, 56.5, 47.1, 43.8, 21.6, 21.0, 14.3; IR (KBr, cm^{-1}) 2919, 1597, 1452, 1344, 1159, 750, 677; HRMS (ESI) m/z: calcd for $C_{40}H_{37}N_3O_4S_2$: M+Na=710.2118; found: 710.2130.

*4.3.13. 5-Benzyl-4′-methyl-1′,7-ditosyl-1′,5,5′,6,7,8-hexahydro-spiro[[1,3]dioxolo[4,5-f]pyrido[3,4-b]indole-9,2′-pyrrole] (**2m**).* Yellow solid; mp: 220–222 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, J=8.0 Hz, 2H), 7.35–7.28 (m, 5H), 7.08–7.05 (m, 4H), 6.72 (d, J=8.0 Hz, 2H), 6.53 (s, 1H), 5.80 (d, J_{ab}=1.2 Hz, 1H), 5.73 (d, J_{ab}=1.2 Hz, 1H), 5.69 (s, 1H), 5.54 (d, J=1.2 Hz, 1H), 5.13 (s, 2H), 4.64 (d, J=14.0 Hz, 1H), 4.41 (d, J_{ab}=13.2 Hz, 1H), 4.28 (d, J_{ab}=13.6 Hz, 1H), 3.95 (d, J_{ab}=12.0 Hz, 1H), 3.88 (d, J_{ab}=12.0 Hz, 1H), 3.80 (d, J=14.0 Hz, 1H), 2.44 (s, 3H), 2.23 (s, 3H), 1.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.3, 144.0, 142.7, 142.3, 136.6, 135.8, 133.6, 131.5, 131.3, 130.6, 130.0, 129.0, 128.4, 127.9, 127.6, 127.5, 127.0, 126.1, 119.8, 110.2, 100.5, 97.6, 90.7, 71.7, 58.8, 54.6, 47.4, 43.1, 21.5, 21.2, 13.9; IR (KBr, cm^{-1}) 2919, 1643, 1466, 1336, 1160, 1035, 757, 666; HRMS (ESI) m/z: calcd for $C_{37}H_{35}N_3O_6S_2$: M+Na=704.1859; found: 704.1871.

*4.3.14. 9′-Benzyl-1,2′-ditosyl-1,1′,2′,3′,4,5,6,7,7a,9′-decahydro-spiro[indole-2,4′-pyrido[3,4-b]indole] (**2n**).* White solid; mp: 212–214 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, J=8.0 Hz, 2H), 7.36–7.28 (m, 5H), 7.12 (d, J=7.2 Hz, 2H), 7.06 (d, J=8.4 Hz, 1H), 6.92–6.86 (m, 3H), 6.48 (d, J=8.0 Hz, 2H), 6.43 (t, J=7.6 Hz, 1H), 6.27 (d, J=8.0 Hz, 1H), 5.45 (s, 1H), 5.28 (d, J_{ab}=16.4 Hz, 1H), 5.20 (d, J_{ab}=16.4 Hz, 1H), 4.66 (d, J=14.0 Hz, 1H), 4.35–4.32 (m, 1H), 3.94 (s, 2H), 3.87 (d, J=14.0 Hz, 1H), 2.89–2.87 (m, 1H), 2.51–2.47 (m, 1H), 2.44 (s, 3H), 2.11 (s, 3H), 2.08–2.07 (m, 1H), 1.93–1.86 (m, 2H), 1.56–1.33 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.0, 142.4, 138.7, 136.8, 136.0, 133.5, 132.8, 130.0, 129.0, 128.1, 127.8, 127.6, 127.0, 126.2, 126.1, 122.6, 120.8, 119.7, 118.8, 109.2, 109.0, 71.8, 60.4, 55.9, 47.1, 42.8, 38.0, 28.1, 26.4, 24.1, 21.6, 21.1, 14.2; IR (KBr, cm^{-1}) 2931, 1598, 1455, 1339, 1159, 754, 660; HRMS (ESI) m/z: calcd for $C_{39}H_{39}N_3O_4S_2$: M+Na=700.2274; found: 700.2295.

*4.3.15. 4′,9-Dimethyl-1′,2-ditosyl-1,1′,2,3,5′,9-hexahydrospiro-[pyrido[3,4-b]indole-4,2′-pyrrole] (**2o**).* Yellow solid; mp: 160–162 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, J=8.0 Hz, 2H), 7.38 (d, J=8.0 Hz, 2H), 7.16 (d, J=8.4 Hz, 1H), 7.07–7.01 (m, 3H), 6.76 (d, J=8.0 Hz, 2H), 6.60 (t, J=7.6 Hz, 1H), 6.50 (d, J=7.6 Hz, 1H), 5.52 (s, 1H), 4.70 (d, J=14.0 Hz, 1H), 4.35 (d, J_{ab}=13.2 Hz, 1H), 4.28 (d, J_{ab}=13.6 Hz, 1H), 3.95–3.85 (m, 3H), 3.62 (d, J=5.2 Hz, 3H), 2.45 (s, 3H), 2.23 (s, 3H), 1.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.0, 142.7, 136.8, 135.9, 133.4, 131.8, 131.4, 129.9, 128.5, 127.6, 127.0, 125.1, 120.9, 119.5, 118.7, 109.8, 108.7, 71.9, 58.6, 54.4, 42.9, 29.7, 21.5, 21.2, 13.9; IR (KBr, cm^{-1}) 2918, 1624, 1450, 1383, 1159, 665; HRMS (ESI) m/z: calcd for $C_{30}H_{31}N_3O_4S_2$: M+Na=584.1648; found: 584.1660.

*4.3.16. 9-Ethyl-4′-methyl-1′,2-ditosyl-1,1′,2,3,5′,9-hexahydro-spiro[pyrido[3,4-b]indole-4,2′-pyrrole] (**2p**).* White solid; mp: 156–158 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, J=8.4 Hz, 2H), 7.39 (d, J=8.0 Hz, 2H), 7.17 (d, J=8.4 Hz, 1H), 7.02–6.98 (m, 3H), 6.69 (d, J=8.0 Hz, 2H), 6.55 (t, J=7.2 Hz, 1H), 6.43 (d, J=8.0 Hz, 1H), 5.54 (s, 1H), 4.69 (d, J=13.6 Hz, 1H), 4.38 (d, J_{ab}=13.2 Hz, 1H), 4.29 (d, J_{ab}=13.6 Hz, 1H), 4.08 (d, J_{ab}=18.0 Hz, 1H), 4.05 (d, J_{ab}=18.0 Hz, 1H), 3.96–3.88 (m, 3H), 2.46 (s, 3H), 2.21 (s, 3H), 1.80 (s, 3H), 1.37 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.0, 142.6, 135.8, 135.5, 133.5, 131.4, 131.2, 130.0, 128.5, 127.6, 126.9, 125.5, 120.8, 119.5, 118.8, 109.5, 108.8, 71.8, 58.7, 54.5, 42.7, 38.2, 21.6, 21.2, 15.5, 13.9; IR (KBr, cm^{-1}) 2919, 1598, 1455, 1338, 1159, 750, 664; HRMS (ESI) m/z: calcd for $C_{31}H_{33}N_3O_4S_2$: M+Na=598.1805; found: 598.1814.

*4.3.17. 9-Allyl-4′-methyl-1′,2-ditosyl-1,1′,2,3,5′,9-hexahydro-spiro[pyrido[3,4-b]indole-4,2′-pyrrole] (**2q**).* Yellow solid; mp: 76–78 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J=8.4 Hz, 2H), 7.38 (d, J=8.0 Hz, 2H), 7.14 (d, J=8.0 Hz, 1H), 7.05–6.99 (m, 3H), 6.73 (d, J=8.0 Hz, 2H), 6.58 (t, J=7.6 Hz, 1H), 6.46 (d, J=7.6 Hz, 1H), 5.97–5.88 (m, 1H), 5.53 (s, 1H), 5.19 (d, J=10.4 Hz, 1H), 4.92 (d, J=17.2 Hz, 1H), 4.64–4.62 (m, 2H), 4.37 (d, J_{ab}=13.6 Hz, 1H), 4.79 (d, J_{ab}=13.2 Hz, 1H), 3.96–3.86 (m, 3H), 3.50–3.45 (m, 1H), 2.46 (s, 3H), 2.22 (s, 3H), 1.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.0, 142.7, 136.1, 135.8, 133.5, 132.6, 131.7, 131.4, 130.0, 128.5, 127.6, 126.9, 125.3, 121.0, 119.7, 118.7, 116.9, 110.1, 109.0, 71.9, 58.6, 54.4, 45.6, 42.8, 21.6, 21.2, 13.9; IR (KBr, cm^{-1}) 2919, 1725, 1596, 1458, 1338, 1160, 751, 662; HRMS (ESI) m/z: calcd for $C_{32}H_{33}N_3O_4S_2$: M+Na=610.1805; found: 610.1812.

*4.3.18. 9-Benzyl-3,4′-dimethyl-2-(4-nitrophenylsulfonyl)-1′-tosyl-1,1′,2,3,5′,9-hexahydrospiro[pyrido[3,4-b]indole-4,2′-pyrrole] (**2r**).* White solid; mp: 152–154 °C; ^{1}H NMR (400 MHz, $CDCl_3$):

δ 8.33 (d, J=8.8 Hz, 2H), 8.15 (d, J=8.8 Hz, 2H), 7.33–7.25 (m, 3H), 7.18 (d, J=8.4 Hz, 1H), 7.09 (d, J=6.4 Hz, 2H), 7.00 (t, J=8.0 Hz, 1H), 6.63–6.55 (m, 4H), 6.43 (d, J=8.0 Hz, 2H), 5.48 (s, 1H), 5.36 (d, J_{ab}=16.8 Hz, 1H), 5.27 (d, J_{ab}=16.8 Hz, 1H), 4.70 (d, J=15.6 Hz, 1H), 4.43 (d, J=15.2 Hz, 1H), 4.29 (d, J_{ab}=15.2 Hz, 1H), 4.22 (d, J_{ab}=15.2 Hz, 1H), 3.48 (dd, J=7.2, 14.0 Hz, 1H), 2.08 (s, 3H), 1.90 (s, 3H), 1.15 (d, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.0, 145.2, 142.1, 136.4, 136.2, 134.2, 129.1, 129.0, 128.1, 127.9, 127.3, 126.6, 126.1, 125.8, 124.1, 121.2, 119.9, 119.0, 109.3, 103.0, 74.0, 65.8, 59.7, 59.2, 47.0, 21.0, 16.2, 14.3; IR (KBr, cm^{-1}) 2989, 1533, 1454, 1348, 1157, 736; HRMS (ESI) m/z: calcd for $C_{36}H_{34}N_4O_6S_2$: M+H=683.1993; found: 683.2004.

*4.3.19. N-(3-(9-benzyl-3-methyl-2-(4-nitrophenylsulfonyl)-2,3-dihydro-1H-pyrido[3,4-b]indol-4(9H)-ylidene)-2-methylallyl)-4-methylbenzenesulfonamide (**2r**–**m**).* Yellow solid; mp: 82–84 °C; 2.65:1 dr value. ^{1}H NMR (400 MHz, $CDCl_3$): δ [7.98 (d, J=8.8 Hz), 7.89 (d, J=8.8 Hz), 2H], 7.79 (d, J=8.4 Hz, 1H), 7.72–7.68 (m, 2H), 7.56 (d, J=8.8 Hz, 1H), 7.32–7.27 (m, 6H), 7.20–7.15 (m, 2H), 7.04–6.96 (m, 3H), 5.33–5.28 (m, 1H), 5.20–5.15 (m, 1H), [5.10 (h), 4.76 (h), 1H], 4.89–4.76 (m, 2H), 4.46–4.37 (m, 1H), 3.74–3.52 (m, 2H), [2.41 (s), 2.38 (s), 3H], [1.83 (s), 1.77 (s), 3H], [1.47 (d, J=6.8 Hz), 1.36 (d, J=6.8 Hz), 3H]; ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.8, 149.6, 144.7, 143.5, 137.2, 136.5, 129.8, 129.1, 128.1, 127.0, 126.4, 126.2, 124.6, 123.9, 123.5, 123.0, 120.6, 119.2, 109.4, 103.9, 101.5, 52.3, 46.9, 46.3, 38.0, 21.4, 20.6, 17.8; IR (KBr, cm^{-1}) 3296, 3062, 2927, 1604, 1530, 1454, 1349, 1159, 1092, 855, 737.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.11.084. These data include MOL files and InChIKeys of the most important compounds described in this article.

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