JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

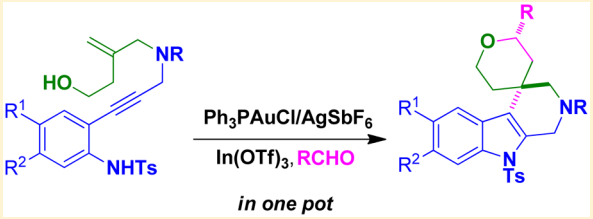
Cooperative Multicatalytic System for the One-Pot Synthesis of Octahydrospiro-β-carbolines

B. V. Subba Reddy,*[†] M. Rajashekhar Reddy,[†] Suresh Yarlagadda,[†] C. Ravikumar Reddy,[†] G. Ravi Kumar,[†] J. S. Yadav,[†] and B. Sridhar[‡]

[†]Natural Product Chemistry, [‡]Laboratory of X-ray Crystallography, CSIR-Indian Institute of Chemical Technology, Hyderabad − 500 007, India

Supporting Information

ABSTRACT: A domino cyclization of 3-((3-(2-aminophenyl)prop-2-ynylamino)methyl)but-3-en-1-ol with aldehydes has been accomplished employing 5 mol % of the $Ph_3PAuCl/AgSbF_6$/$In(OTf)_3$ system to afford the corresponding octahydrospiro[pyran-4,4′-pyrido[3,4-*b*]indole] derivatives in good yields with high selectivity. This is the first report on the synthesis of spiro-β-carbolines through a multicatalytic cascade process.



Tetrahydro-β-carbolines (THBC) are often found in naturally occurring indole alkaloids and are considered as privileged scaffolds in medicinal chemistry.[1,2] Owing to their inherent biological properties, several efforts have been made to generate the diversified THBCs through a Pictet−Spengler reaction of tryptophan or tryptamine with aliphatic or aromatic aldehydes under acidic conditions.[3] In particular, spiro-THBCs are important pharmacopores and found in several pharmaceuticals (Figure 1).[4] For example, spiro-indolinone, i.e., NITD609, is a potent antimalarial lead in nanomolar scale and kills the blood strain of *Plasmodium falciparum*.[5] However, only a few methods have been developed for the synthesis of spiro-THBCs.[6] Therefore, the development of a one-pot strategy for the synthesis of spiro-THBCs is enviable to generate structural complexity and diversity for drug discovery.

Recently, domino cyclization of 2-alkynylanilines has become a powerful synthetic route for the synthesis of indoles and quinolines.[7] A large number of reagents are reported for the conversion of 2-alkynylanilines into 2-substituted indoles. Among them, Au complexes are well explored for the above transformation due to their high alkynophilicity and Lewis acidity to promote further C−C or C−X bond formation.[8,9] Inspired by recent advancement in multicatalytic systems,[10] we herein disclose a novel cascade strategy for the one-pot synthesis of octahydrospiro[pyran-4,4′-pyrido[3,4-*b*]indole] derivatives from 3-((3-(2-aminophenyl)prop-2-ynylamino)methyl)but-3-en-1-ol and aldehydes through a multicatalytic cascade cyclization.

At the outset, we attempted the coupling of 3-((3-(2-aminophenyl)prop-2-ynylamino)methyl)but-3-en-1-ol (**7a**) with benzaldehyde using 5 mol % of the $Ph_3PAuCl/AgSbF_6$ catalytic system. Though the $Ph_3PAuCl/AgSbF_6$ system facilitates the cycloisomerization of 2-alkynylaniline, it did not show much catalytic effect in subsequent cyclization (Table 1, entry i). These initial findings turned our attention to find the more effective catalytic system. As a result, we performed a systematic screening of various catalysts to obtain the desired product. However, no desired cyclization was observed with several Lewis acids such as $InCl_3$, $FeCl_3$, $Sc(OTf)_3$, $In(OTf)_3$, $BF_3.OEt_2$, and TMSOTf (Table 1, entries a−f). Similarly, $AgSbF_6$ alone or in combination with $In(OTf)_3$ failed to give the target product (Table 1, entries g and h). Furthermore, the use of $Ph_3PAuCl/AgSbF_6$ in combination with binol phosphoric acid also failed to provide the desired product (Table 1, entry j).

After screening several catalysts, the $Ph_3PAuCl/AgSbF_6$/$In(OTf)_3$ catalyst system was found to be the best to afford the desired product (Table 1, entries k and l). In the above catalytic system, Au(I) activates the alkyne moiety to promote the cycloisomerization and Ag(I) is expected to increase the rate of reaction by generating Au(I) cationic species after liberating AgCl. $In(OTf)_3$ is highly oxophilic, and hence, it activates the aldehyde effectively. Therefore, the synergism between these catalysts facilitates the desired domino cyclization. As shown in Table 1, the combination of 5 mol % of each catalyst gave the product **8a** in 80% after 2.0 h in dichloromethane at 25 °C (Table 1, entry l). No further improvement in yield of **8a** was observed by elevating the temperature to 40 °C. In addition, there was no much difference in yield when the reaction was performed using either 10 mol % or 5 mol % of each catalyst (Table 1). Inspired by the above results, we extended this method to different aldehydes. Interestingly, a large number of aldehydes including aromatic, heteroaromatic, and aliphatic participated well in this domino process. As shown in Table 2, the substituent present on the aromatic ring had shown some effect on the conversion. Indeed, electron-rich aldehydes gave the product relatively in higher yields than electron-deficient substrates. Furthermore, a heterocyclic substrate, i.e., thiophene-2-carboxaldehyde, gave the product in good yields (Table 2,

Received: May 18, 2015
Published: August 7, 2015

DOI: 10.1021/acs.joc.5b01108
J. Org. Chem. 2015, 80, 8807−8814

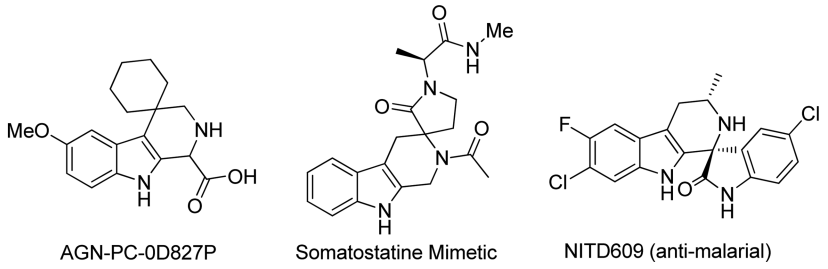
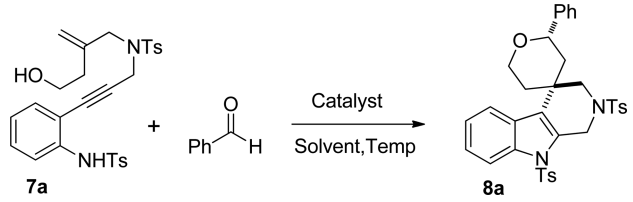


Figure 1. Examples of biologically active spirocycles.

Table 1. Optimization of the Catalytic System in the Formation of 8a



entry	Lewis acid	equiv	solvent	temp (°C)	time (h)	yield (%)[a]	dr[b]
a	ln CI_3	0.1	DCM	0 to 40	4	nd	
b	$FeCI_3$	0.1	DCM	0 to 40	4	nd	
c	$Sc(OTf)_3$	0.1	DCM	0 to 40	4	nd	
d	$ln(OTf)_3$	0.1	DCM	0 to rt	4	nd	
e	$BF_3{\cdot}OEt_2$	1.1	DCM	0 to rt	4	nd	
f	TMSOTf	1.1	DCM	−40 to rt	4	nd	
g	$AgSbF_6$	0.1	DCM	0 to rt	4	nd	
h	$ln(OTf)_3/AgSbF_6$	0.1	DCM	0 to rt	4	nd	
i	$PPh_3AuCI/AgSbF_6$	0.1	DCM	0 to rt	4	nd	
j	$PPh_3AuCI/AgSbF_6$/BINOLPA	0.1	DCM	0 to rt	4	nd	
k	$PPh_3AuCI/AgSbF_6/ln(OTf)_3$	0.1	DCM	0 to rt	1.5	80	100:0
l	$PPh_3AuCI/AgSbF_6/ln(OTf)_3$	0.05	DCM	0 to rt	2.0	80	100:0

[a]Yield refers to pure products after column chromatography. [b]Ratio of products was determined by ^1H NMR. nd = no desired product.

entries e and s). However, aliphatic aldehydes afforded the spiro-*β*-carbolines comparatively in lower yields than aromatic and heterocyclic substrates. In addition, we studied the effect of a *para*-methyl substituent with respect to the amino group and alkyne moiety, and the results are present in Table 2 (entries v and w). The scope of the reaction is further illustrated with respect to ketones such as cyclohexanone, *N*-benzylisatin, and tetralone. Although the reaction was successful with cyclohexanone, other substrates such as *N*-benzylisatin and tetralone failed to undergo domino cyclization (Table 2, entries x and y).

Remarkably, acid-sensitive substrates like phenylacetaldehyde and *α,β*-unsaturated aldehydes also gave the desired products reasonably in good yields (Table 2, entries c, n, and p). Furthermore, this method also works efficiently with sterically hindered substrates, for example, naphthaldehyde (Table 2, entry q). Therefore, a wide array of octahydrospiro[pyran-4,4′-pyrido[3,4-*b*]-indole] scaffolds were prepared by using this protocol (Table 2). The structure of **8a** was established by ^1H and ^{13}C NMR data, and the relative stereochemistry of **8a** was determined by single-crystal X-ray diffraction (Figure A, Supporting Information).[11] The stereochemistry of all other products was determined by analogy of NMR data with **8a**. In addition, the stereochemistry of **8r** was confirmed by 2D DQFCOSY and NOESY studies (Figure B, Supporting Information).

A plausible reaction mechanism is shown in Scheme 1. The reaction proceeds likely via the coordination of cationic Au(I) species with an alkyne moiety to generate the Au-*π* complex **A**, and subsequent attack of the tethered amino group gives the cyclic intermediate **B**. Simultaneously, the pendent alcohol reacts with aldehyde activated likely by In(III) to afford the *E*-oxocarbenium ion **C**. Further attack of the internal olefin generates the tetrahydropyranyl cation **D**, which is trapped intramolecularly by indole to produce the spiro[pyran-4,4′-pyrido[3,4-*b*]indole] **8** with regeneration of the gold catalyst (Scheme 1).

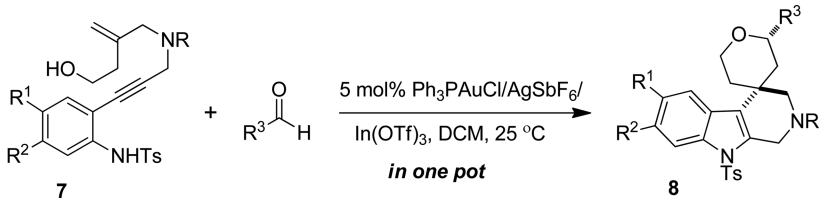
In summary, a novel one-pot strategy has been developed for the synthesis of octahydrospiro[pyran-4,4′-pyrido[3,4-*b*]indole] scaffolds through a multicatalytic cascade cyclization. This method facilitates the formation of sequential C−N, C−O, and two C−C bond formations with a wide substrate scope under relatively mild and neutral conditions, which makes it an attractive strategy. This strategy also illustrates the cooperative catalysis of Au/Ag/In complexes for tandem processes.

EXPERIMENTAL SECTION

General. All the solvents were dried according to standard literature procedures. Reactions were performed in an oven-dried round-bottom flask, the flasks were fitted with rubber septa, and reactions were conducted under a nitrogen atmosphere. Glass syringes were used to transfer solvent. Crude products were purified by column chromatography on silica gel of 60−120 or 100−200 mesh. Thin-layer chromatography plates were visualized by exposure to ultraviolet light and/or by exposure to iodine vapors and/or by exposure to a methanolic acidic solution of *p*-anisaldehyde, followed by heating (<1 min) on a

DOI: 10.1021/acs.joc.5b01108
J. Org. Chem. 2015, 80, 8807−8814

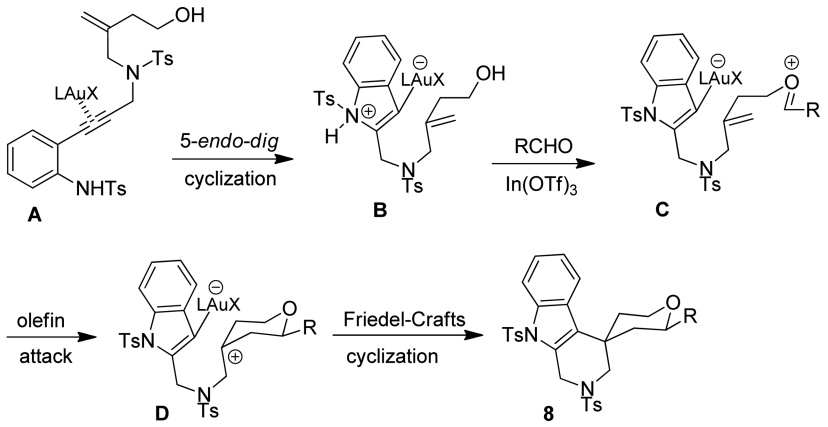
Table 2. One-Pot Synthesis of Spiro[pyran-4,4′-pyrido[3,4-*b*]indole] Derivatives[a,b]



entry	R	R^1	R^2	aldehyde	time (h)	product (**8**)	yield (%)[a]
a	Ts	H	H	benzaldehyde	2.0	**8a**	80
b	Ns	H	H	4-bromobenzaldehyde	2.0	**8b**	75
c	Ns	H	H	2-phenylacetaldehyde	1.0	**8c**	69
d	Ns	H	H	hexanal	1.0	**8d**	68
e	Ns	H	H	thiophene-2-carbaldehyde	2.0	**8e**	78
f	Ns	H	H	3-methylbenzaldehyde	2.0	**8f**	81
g	Ns	H	H	3-fluorobenzaldehyde	2.0	**8g**	83
h	Ns	H	H	3-chlorobenzaldehyde	2.0	**8h**	80
i	Ns	H	H	cyclohexanone	3.0	**8i**	75
j	Ts	H	H	2-methylbenzaldehyde	1.0	**8j**	79
k	Ts	H	H	2-chlorobenzaldehyde	2.0	**8k**	75
l	Ts	H	H	4-methoxybenzaldehyde	3.0	**8l**	85
m	Ts	H	H	3-methylbutanal	1.0	**8m**	63
n	Ts	H	H	cyclocitral	2.0	**8n**	78
o	Ts	H	H	4-nitrobenzaldehyde	1.0	**8o**	64
p	Ts	H	H	cinnamaldehyde	2.0	**8p**	78
q	Ns	H	H	1-naphthaldehyde	2.0	**8q**	83
r	Ts	Cl	H	4-methoxybenzaldehyde	3.0	**8r**	82
s	Ts	Cl	H	thiophene-2-carbaldehyde	2.0	**8s**	80
t	Ts	Cl	H	3,4,5-trimethoxybenzaldehyde	6.0	**8t**	88
u	Ts	Cl	H	3,4-dimethoxybenzaldehyde	5.0	**8u**	86
v	Ts	CH_3	H	4-bromobenzaldehyde	2.0	**8v**	75
w	Ts	H	CH_3	4-bromobenzaldehyde	2.0	**8w**	75
x	Ns	H	H	*n*-benzylisatin	6.0		
y	Ns	H	H	*α*-tetralone	6.0		

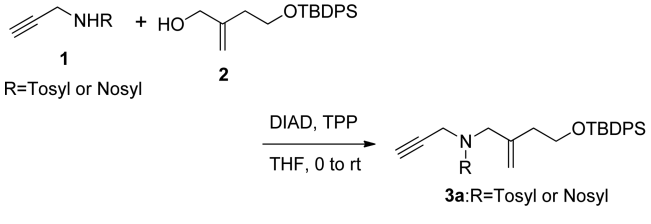
[a]Yield refers to pure products after column chromatography. [b]Ratio of the products was determined by ^{1}H NMR.

Scheme 1. A Plausible Reaction Pathway



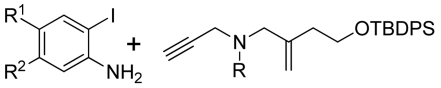
hot plate (~250 °C). Organic solutions were concentrated on a rotary evaporator at 35−40 °C. IR spectra were recorded on an FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR (proton-decoupled) spectra were recorded in $CDCl_3$ solvent on a 200, 300, 400, or 500 MHz NMR spectrometer. Chemical shifts (δ) were reported in parts per million (ppm) with respect to TMS as an internal standard. Coupling constants (J) are quoted in hertz (Hz). Mass spectra were recorded on a mass spectrometer by the electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI) technique.

Experimental Procedures and Spectral Data.



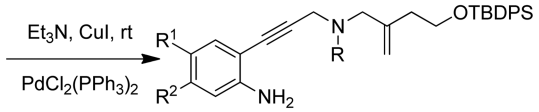
DOI: 10.1021/acs.joc.5b01108
J. Org. Chem. 2015, 80, 8807−8814

*N-(4-((tert-Butyldiphenylsilyl)oxy)-2-methylenebutyl)-4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide (**3a**).* To a stirred solution of **1** (0.150 g, 0.717 mmol), **2** (0.244 g, 0.717 mmol), and triphenylphosphine (0.207 g, 0.789 mmol) in THF (3 mL) at 0 °C was added diethyl azodicarboxylate (0.159 g, 0.789 mmol) dropwise over 2 min. The resulting mixture was stirred at room temperature for overnight. After completion of the reaction, as indicated by TLC, the solvent was evaporated on a rotary evaporator and the resulting crude mixture was purified by column chromatography (silica gel, 60−120 mesh) using an ethyl acetate/*n*-hexane gradient mixture to afford the pure product (**3a**) 0.331 g, 87% yield, as a pale yellow thick liquid, ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72−7.63 (m, 6H), 7.44 (m, 5H), 7.29−7.25 (m, 3H), 5.09 (s, 3H), 5.04 (s, 1H), 4.03 (d, J = 2.2 Hz, 2H), 3.8 (t, J = 6.4 Hz, 2H), 3.7 (s, 3H), 2.42 (s, 3H), 2.31 (t, J = 6.4 Hz, 2H), 1.92 (t, J = 2.2 Hz, 1H), 1.04 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.4, 139.9, 135.8, 135.5, 133.7, 129.5, 129.3 127.8, 127.6, 116.6, 76.2, 73.7, 61.9, 51.1, 35.9, 35.4, 26.8, 21.5, 19.1. MS (ESI) m/z 549 $[M + NH_4]^+$; HRMS: Exact mass calcd for $C_{31}H_{41}O_3N_2SSi$ $[M + NH_4]^+$: 549.2601. Found: 549.2612.



4a:R^1=H
4b:R^1=Cl
4c:R^1=CH_3
4d:R^2=CH_3

3a:R=Tosyl or Nosyl



5a:R=Tosyl,R^1=H,R^2=H
5b:R=Tosyl,R^1=Cl,R^2=H
5c:R=Tosyl,R^1=CH_3,R^2=H
5d:R=Tosyl,R^1=H,R^2=CH_3

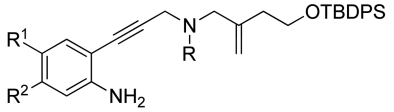
*N-(3-(2-Aminophenyl)prop-2-yn-1-yl)-N-(4-((tert-butyldiphenylsilyl)oxy)-2-methylenebutyl)-4-methylbenzenesulfonamide (**5a**).* A mixture of 2-iodoaniline (0.331 g, 1.511 mmol) and Et_3N (1 mL) in THF (2 mL) was degassed with nitrogen. $PdCl_2(PPh_3)_2$ (52 mg, 5 mol %), copper iodide (14 mg, 5 mol %), and alkyne **3** (0.963 g, 1.81 mmol) were added at room temperature. The mixture was stirred for 8 h at the same temperature. After completion of the reaction, as indicated by TLC, the mixture was filtered through a short pad of Celite, the solvent was evaporated on a rotary evaporator, and the resulting crude product was purified by column chromatography (silica gel, 60−120 mesh) using an ethyl acetate/*n*-hexane gradient mixture to afford the pure product in (0.714 g, 76%) yield as a black thick mass.

*N-(3-(2-Aminophenyl)prop-2-yn-1-yl)-N-(4-((tert-butyldiphenylsilyl)oxy)-2-methylenebutyl)-4-methylbenzenesulfonamide (**5a**).* 0.714 g, 76% yield, black thick mass, ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 (d, J = 8.0 Hz, 2H), 7.69−7.65 (m, 4H), 7.45−7.36 (m, 7H), 7.24 (d, J = 8.0 Hz, 1H), 7.09−7.05 (m, 1H), 6.84 (dd, J = 1.2, 7.6 Hz, 1H), 6.62−6.56 (m, 2H), 5.12 (s, 1H), 5.05 (s, 1H), 4.27 (s, 2H), 3.9 (bs, 2H), 3.82 (t, J = 6.2 Hz, 2H), 3.77 (s, 2H), 2.36−2.32 (m, 5H), 1.04 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.8, 143.4, 140.1, 135.7, 135.5, 133.7, 132.0, 129.6, 129.5, 129.4, 127.6, 127.5, 117.3, 116.6, 114.0, 106.6, 87.7, 82.4, 61.8, 51.4, 36.4, 35.8, 29.6, 26.8, 21.3, 19.1. MS (ESI) m/z 623 $[M + H]^+$; HRMS: Exact mass calcd for $C_{37}H_{43}O_3N_2SSi$ $[M + H]^+$: 623.2758. Found: 623.2773.

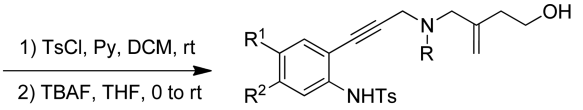
*N-(3-(2-Amino-5-chlorophenyl)prop-2-yn-1-yl)-N-(4-((tert-butyldiphenylsilyl)oxy)-2-methylenebutyl)-4-methylbenzenesulfonamide (**5b**).* 0.644 g, yield 75%, black thick mass, ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (d, J = 8.3 Hz, 1H), 7.67 (dd, J = 2.2, 8.3 Hz, 3H), 7.48−7.35 (m, 7H), 7.3−7.27 (m, 1H), 7.05−6.99 (dd, J = 2.2, 8.3 Hz, 1H), 6.7−6.67 (m, 1H), 6.54 (d, J = 8.3 Hz, 1H), 5.11 (s, 1H), 5.06 (s, 1H), 4.25 (s, 2H), 3.96 (bs, 2H), 3.82 (t, J = 6.0 Hz, 2H), 3.76 (s, 2H), 2.40 (s, 3H), 2.34 (t, J = 6.0 Hz, 2H), 1.05 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.5, 143.7, 140.1, 135.5, 135.5, 133.7, 131.3, 129.6, 129.5, 127.7, 127.6, 121.6, 116.7, 115.2, 107.9, 87.9, 81.2, 70.0, 61.9, 51.5, 36.3, 35.9, 26.8, 21.9, 21.4, 19.1. MS (ESI) m/z 657 $[M + H]^+$; HRMS: Exact mass calcd for $C_{37}H_{42}O_3ClN_2SSi$ $[M + H]^+$: 657.2368. Found: 657.2384.

*N-(3-(2-Amino-5-methylphenyl)prop-2-yn-1-yl)-N-(4-((tert-butyldiphenylsilyl)oxy)-2-methylenebutyl)-4-methylbenzenesulfonamide (**5c**).* 0.740 g, yield 82%, black thick mass, ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 (d, J = 8.2 Hz, 2H), 7.68−7.65 (m, 4H), 7.44−7.36 (m, 8H), 7.24 (s, 1H), 6.65−6.63 (m, 1H), 6.53 (d, J = 8.0 Hz, 1H), 5.12 (s, 1H), 5.05 (s, 1H), 4.27 (s, 2H), 3.82 (t, J = 6.0 Hz, 2H), 3.76 (s, 2H), 2.36−2.32 (m, 5H), 2.17 (s, 3H), 1.05 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.5, 143.4, 140.1, 135.9, 135.5, 133.8, 132.2, 130.5, 129.5, 129.5, 127.7, 127.6, 116.6, 114.3, 86.5, 82.7, 77.2, 61.9, 51.4, 36.5, 35.9, 26.8, 21.4, 20.0, 19.2. MS (ESI) m/z 637 $[M + H]^+$; HRMS: Exact mass calcd for $C_{38}H_{45}O_3N_2SSi$ $[M + H]^+$: 637.2915. Found: 637.2919.

*N-(3-(2-Amino-4-methylphenyl)prop-2-yn-1-yl)-N-(4-((tert-butyldiphenylsilyl)oxy)-2-methylenebutyl)-4-methylbenzenesulfonamide (**5d**).* 0.713 g, yield 79%, black thick mass, ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (d, J = 8.3 Hz, 2H), 7.68−7.64 (m,, 4H), 7.45−7.35 (m, 8H), 7.24 (d, J = 8.0 Hz, 1H), 6.73 (d, J = 7.7 Hz, 1H), 6.44−6.39 (m, 2H), 5.11 (s, 1H), 5.06 (s, 1H), 4.25 (s, 2H), 3.82 (t, J = 6.3 Hz, 2H), 3.76 (s, 2H), 2.36−2.31 (m, 5H), 2.23 (s, 3H), 1.05 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.7, 143.4, 140.1, 140.0, 135.8, 135.5, 133.7, 132.0, 129.5, 129.4, 127.3, 127.6, 118.6, 116.6, 114.7, 104.0, 86.2, 82.6, 61.9, 51.5, 36.5, 35.9, 26.8, 21.5, 21.4, 19.1. MS (ESI) m/z 637 $[M + H]^+$; HRMS: Exact mass calcd for $C_{38}H_{45}O_3N_2SSi$ $[M + H]^+$: 637.2915. Found: 637.2920.



5a:R=Tosyl,R^1=H,R^2=H
5b:R=Tosyl,R^1=Cl,R^2=H
5c:R=Tosyl,R^1=CH_3,R^2=H
5d:R=Tosyl,R^1=H,R^2=CH_3
5e:R=Nosyl,R^1=H,R^2=H



7a:R=Tosyl,R^1=H,R^2=H
7b:R=Tosyl,R^1=Cl,R^2=H
7c:R=Tosyl,R^1=CH_3,R^2=H
7d:R=Tosyl,R^1=H,R^2=CH_3
7e:R=Nosyl,R^1=H,R^2=H

To a stirred solution of **5** (0.714 g, 1.147 mmol) and tosyl chloride (0.240 g, 1.262 mmol) in DCM (5 mL) at 0 °C was added pyridine (0.099 mL, 1.262 mmol) dropwise. The resulting mixture was allowed to stir at rt for overnight. After completion of the reaction, as indicated by TLC, the mixture was extracted with DCM and it was used directly for the next step, To a stirred solution of **6** (0.998 g,1.286 mmol) in THF (8 mL) at 0 °C was added TBAF (0.403 mL, 1.543 mmol) dropwise, and the resulting mixture was allowed to stir at rt for 2 h. After completion of the reaction, as indicated by TLC, the mixture was quenched with a sat. solution of $NaHCO_3$ and the aqueous layer was extracted with ethyl acetate. Removal of the solvent, followed by purification on silica gel column chromatography (silica gel, 60−120 mesh) using an ethyl acetate/*n*-hexane gradient mixture, afforded the pure product 7 in (0.567 g, 82%) yield as a colorless thick liquid.

*N-(4-Hydroxy-2-methylenebutyl)-4-methyl-N-(3-(2-(4-methylphenylsulfonamido)phenyl)prop-2-yn-1-yl)benzenesulfonamide (**7a**).* 0.567 g, 82% yield, pale yellow liquid, ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 (dd, J = 0.6, 8.2 Hz, 1H), 7.68−7.65 (m, 2H), 7.62−7.59 (m, 2H), 7.36−7.34 (m, 1H), 7.25−7.18 (m, 5H), 6.49−6.47 (m, 1H), 4.89 (s, 1H), 4.86 (s, 1H), 4.82 (d, J = 1.0 Hz, 2H), 3.95 (s, 2H), 3.65 (t, J = 6.2 Hz, 2H), 2.41 (s, 3H), 2.34 (s, 3H), 2.21 (t, J = 6.2 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.0, 143.5, 140.5, 137.2, 136.8, 136.2, 135.3, 129.8, 129.6, 129.3, 127.3, 126.3, 124.4, 123.7, 120.7, 116.4, 114.5, 111.3, 60.6, 53.2, 45.6, 36.0, 21.4, 21.4; MS (ESI) m/z 539

DOI: 10.1021/acs.joc.5b01108
J. Org. Chem. 2015, 80, 8807−8814

$[M + H]^+$; HRMS: Exact mass calcd for $C_{28}H_{31}O_5N_2S_2$ $[M + H]^+$: 539.1669. Found: 539.1675.

*N-(3-(5-Chloro-2-(4-methylphenylsulfonamido)phenyl)prop-2-yn-1-yl)-N-(4-hydroxy-2-methylenebutyl)-2-nitrobenzenesulfonamide (**7b**).* 0.498 g, yield 80%, pale yellow liquid, ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.0 (d, J = 8.3 Hz, 1H), 7.83 (d, J = 7.9 Hz, 1H), 7.64 (d, J = 8.5 Hz, 2H), 7.57−7.6 (m, 1H), 7.54 (td, J = 15.4, 7.4, 1.3 Hz, 1H), 7.30 (d, J = 7.7 Hz, 1H), 7.24−7.28 (m, 2H), 7.20 (d, J = 8.0 Hz, 2H), 7.15−7.19 (m, 1H), 6.5 (s, 1H), 4.98 (s, 4H), 4.20 (s, 2H), 3.60 (t, J = 12.2 Hz, 2H), 2.30 (s, 3H), 2.20 (t, J = 12.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.4, 145.1, 140, 137.1, 135.1, 135.1, 133.6, 133.3, 131.5, 130.6, 129.9, 129.1, 126.3, 124.6, 123.9, 123.7, 120.7, 116, 114.4, 111, 60.4, 53.0, 45.1, 35.9, 21.5. MS (ESI) m/z 573 $[M + H]^+$; HRMS: Exact mass calcd for $C_{28}H_{30}O_5ClN_2S_2$ $[M + H]^+$: 573.1279. Found: 573.1296.

*N-(4-Hydroxy-2-methylenebutyl)-4-methyl-N-(3-(5-methyl-2-(4-methylphenylsulfonamido)phenyl)prop-2-yn-1-yl)benzenesulfonamide (**7c**).* 0.508 g, yield 82%, pale yellow liquid, ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90 (d, J = 8.5 Hz, 1H), 7.66 (d, J = 8.0 Hz, 2H), 7.58 (d, J = 8.2 Hz, 2H), 7.27−7.23 (m, 1H), 7.19 (d, J = 8.2 Hz, 2H), 7.12 (s, 1H), 7.06 (d, J = 8.3 Hz, 1H), 6.40 (s, 1H), 4.87 (d, J = 16.6 Hz, 1H), 4.80 (s, 2H), 3.93 (s, 2H), 3.66 (t, J = 6.2 Hz, 2H), 2.41 (s, 3H), 2.37 (s, 3H), 2.33 (s, 3H), 2.21 (t, J = 6.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.8, 143.5, 140.4, 136.8, 136.2, 135.4, 135.2, 133.3, 129.7, 129.6, 127.2, 126.2, 125.8, 120.6, 116.4, 114.2, 111.3, 60.6, 53.1, 45.6, 35.9, 21.5, 21.4, 21.1. MS (ESI) m/z 553 $[M + H]^+$; HRMS: Exact mass calcd for $C_{29}H_{33}N_2O_5S_2$ $[M + H]^+$: 553.1825. Found: 553.1830.

*N-(4-Hydroxy-2-methylenebutyl)-4-methyl-N-(3-(4-methyl-2-(4-methylphenylsulfonamido)phenyl)prop-2-yn-1-yl)benzenesulfonamide (**7d**).* 0.508 g, yield 82%, pale yellow liquid, ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85 (s, 1H), 7.56 (d, J = 8.2 Hz, 2H), 7.58 (d, J = 8.3 Hz, 2H), 7.25−7.18 (m, 4H), 7.02 (d, J = 8.3 Hz,1H), 6.40 (s, 1H), 4.9 (s, 1H), 4.85 (s, 1H), 4.8 (s, 2H), 3.93 (s, 2H), 3.66 (t, J = 6.2 Hz, 2H), 2.45 (s, 3H), 2.40 (s, 3H), 2.34 (s, 3H), 2.21 (t, J = 6.2 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.9, 143.4, 140.1, 135.5, 133.8, 132.2, 130.5, 129.5, 129.5, 127.7, 127.6, 116.6, 114.3, 86.5, 82.7, 77.2, 61.9, 51.4, 36.5, 35.8, 26.8, 21.4, 20.2, 19.2. MS (ESI) m/z 553 $[M + H]^+$; HRMS: Exact mass calcd for $C_{29}H_{33}N_2O_5S_2$ $[M + H]^+$: 553.1825. Found: 553.1830.

*N-(4-Hydroxy-2-methylenebutyl)-N-(3-(2-(4-methylphenylsulfonamido)phenyl)prop-2-yn-1-yl)-3-nitrobenzenesulfonamide (**7e**).* yield 0.522 g, yield 84%, pale yellow liquid, ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (d, J = 9.0 Hz, 1H), 7.66 (d, J = 8.3 Hz, 2H), 7.58 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 1.9 Hz, 1H), 7.28−7.19 (m, 5H), 6.43 (s, 1H), 4.9 (s, 1H), 4.85 (s, 1H), 4.8 (s, 2H), 3.93 (s, 2H), 3.66 (t, J = 6.2 Hz, 2H), 2.41 (s, 3H), 2.36 (s, 3H), 2.21 (t, J = 6.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.3, 143.7, 140.3, 136.5, 136.4, 134.9, 131.6, 130.5, 129.9, 129.6, 129.6, 127.2, 126.2, 124.5, 120.2, 116.6, 115.4, 110.4, 60.5, 53.3, 45.5, 36.2, 35.8, 21.9, 21.8, 21.5, 21.4. MS (ESI) m/z 570 $[M + H]^+$; HRMS: Exact mass calcd for $C_{27}H_{28}O_7N_3S_2$ $[M + H]^+$: 570.1363. Found: 570.1370.

*General Procedure for the Synthesis of 2-(Naphthalen-1-yl)-2′-((2-nitrophenyl)sulfonyl)-9′-tosyl-1′,2,2′,3,3′,5,6,9′-octahydrospiro-[pyran-4,4′-pyrido[3,4-b]indole] (**8**).* To a solution of *N*-(4-hydroxy-2-methylene butyl)-*N*-(3-(2-(4-methylphenylsulfonamido)phenyl)prop-2-yn-1-yl)-2-nitrobenzenesulfonamide (**7b**) (0.1 g, 1 equiv) and aldehyde (1.5 equiv) in anhydrous DCM (3 mL) were added Ph_3PAuCl + $AgSbF_6$ + $In(OTf)_3$ (5 mol % each) at 0 °C. The resulting mixture was allowed to stir at room temperature under a nitrogen atmosphere for the specified time (Table 2). After completion, the reaction mass was quenched with $NaHCO_3$ solution (5 mL) and then extracted with dichloromethane (2 × 5 mL). The organic phases were washed with brine (2 × 5 mL), dried over anhydrous Na_2SO_4, and concentrated on a rotary evaporator. The resulting crude product was purified by silica gel column chromatography (60−120 mesh) using an ethyl acetate/hexane gradient mixture to afford the product **8** (Table 2).

Characterization Data of Products. *2-Phenyl-2′,9′-ditosyl-1′,2,2′,3,3′,5,6,9′-octahydrospiro[pyran-4,4′-pyrido[3,4-b]indole] (**8a**, Table 2, entry a).* 0.093 g, yield 80%, white solid, mp 132 °C, ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.12−8.10 (m, 1H), 8.08 (d, J = 8.2 Hz, 1H), 7.86−7.83 (m, 2H), 7.72 (d, J = 7.7 Hz, 1H), 7.68−7.65 (m, 2H), 7.48 (t, J = 7.7 Hz, 1H), 7.44−7.41 (m, 2H), 7.40−7.37 (m, 2H), 7.34−7.30 (m, 2H), 7.24−7.20 (m, 3H), 4.72−4.65 (m, 2H), 4.54 (d, J = 16.1 Hz, 1H), 4.16 (dd J = 4.5, 12.0 Hz, 1H), 3.92 (td, J = 1.9, 12.8 Hz, 1H), 3.73 (d, J = 12.2 Hz, 1H), 3.4 (d, J = 12.2 Hz, 1H), 2.63 (td, J = 5.3, 13.5 Hz, 1H), 2.48 (s, 3H), 2.33 (s, 3H), 2.32−2.27 (m, 1H), 1.90 (d, J = 14.0 Hz, 1H), 1.59 (d, J = 14.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.2, 144.0, 142.1, 136.2, 135, 133.9, 133.6, 130.0, 128.4, 128.3, 127.4, 127.0, 126.4, 125.6, 124.3, 123.2, 123.0, 120.2, 114.4, 75.1, 64.1, 50.2, 45.3, 40.4, 36.1, 32.0, 21.5. MS (ESI) m/z 627 $[M + H]^+$; HRMS: Exact mass calcd for $C_{35}H_{35}O_5N_2S_2$ $[M + H]^+$: 627.1986. Found: 627.1992.

*2-(4-Bromophenyl)-2′-((2-nitrophenyl)sulfonyl)-9′-tosyl-1′,2,2′,3,3′,5,6,9′-octahydrospiro[pyran-4,4′-pyrido[3,4-b]indole] (**8b**, Table 2, entry b).* 0.0968 g, yield 75%, white solid, mp 225 °C, ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.18−8.14 (m, 1H), 8.08 (d, J = 8.2 Hz, 1H), 7.83−7.77 (m, 2H), 7.75−7.68 (m, 4H), 7.45−7.41 (m, 2H), 7.32−7.22 (m, 6H), 4.96 (d, J = 16.7 Hz, 1H), 4.75−4.68 (m, 2H), 4.21−4.12 (m, 2H), 3.94 (td, J = 1.8, 12.6 Hz, 1H), 3.61 (d, J = 13.4 Hz, 1H), 2.68 (td, J = 5.3, 13.5 Hz, 1H), 2.34 (s, 3H), 2.25−2.17 (m, 1H), 1.93 (d, J = 14.1 Hz, 1H), 1.6−1.57 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.2, 145.3, 141.2, 136.1, 134.7, 134.0, 132.0, 131.8, 131.3,130.8, 130.1, 129.6, 127.2, 120.9, 126.4, 124.5, 124.3, 123.4, 123.0, 121.0, 120.2, 114.4, 74.3, 64.0, 50.3, 44.9, 36.1, 32.1, 21.5. MS (ESI) m/z 736 $[M + H]^+$; HRMS: Exact mass calcd for $C_{34}H_{31}O_7N_3BrS_2$ $[M + H]^+$: 736.0781. Found: 736.0797

*2-Benzyl-2′-((2-nitrophenyl)sulfonyl)-9′-tosyl-1′,2,2′,3,3′,5,6,9′-octahydrospiro[pyran-4,4′-pyrido[3,4-b]indole] (**8c**, Table 2, entry c).* 0.081 g, yield 69%, white solid, mp 92 °C, ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.12−8.08 (m, 2H), 7.79−7.75 (m, 2H), 7.73−7.67 (m, 4H), 7.33−7.19 (m, 9H), 4.97−4.90 (m, 1H), 4.85 (d, J = 16.4 Hz, 1H), 4.70 (d, J = 16.4 Hz, 1H), 4.12−4.04 (m, 1H), 3.95 (dd, J = 4.7, 12.2 Hz, 1H), 3.9−3.82 (m, 2H), 3.73 (t, J = 11.4 Hz, 1H), 3.57 (d, J = 13.2 Hz, 1H), 2.90 (dd, J = 7.1, 13.8 Hz, 1H), 2.69 (dd, J = 7.1, 13.8 Hz, 1H), 2.36 (s, 3H), 2.23−2.15 (m, 1H), 1.65−1.51 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.2, 145.3, 138.0, 136.1, 134.9, 133.9, 131.9, 131.7, 130.7, 130.0, 129.9, 129.8, 129.5, 129.3, 128.1, 127.0, 126.5, 126.3, 126.2, 124.4, 124.3, 123.2, 120.4, 114.3, 73.5, 63.6, 50.4, 44.8, 42.7, 38.0, 35.7, 31.9, 21.5. MS (ESI) m/z 672 $[M + H]^+$; HRMS: Exact mass calcd for $C_{35}H_{34}O_7N_3S_2$ $[M + H]^+$: 672.1832. Found: 672.1841

*2′-((2-Nitrophenyl)sulfonyl)-2-pentyl-9′-tosyl-1′,2,2′,3,3′,5,6,9′-octahydrospiro[pyran-4,4′-pyrido[3,4-b]indole] (**8d**, Table 2, entry d).* 0.0777 g, yield 68%, white solid, mp 105 °C, ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.15−8.09 (m, 2H), 7.8−7.77 (m, 2H), 7.75−7.69 (m, 4H), 7.32−7.28 (m, 1H), 7.27−7.22 (m, 3H), 4.80 (d, J = 16.7 Hz, 2H), 3.96 (dd, J = 4.4, 12.3 Hz, 1H), 3.8−3.69 (m, 3H), 3.59−3.52 (m, 1H), 2.45 (td, J = 5.1, 13.5 Hz, 1H), 2.36 (s, 3H), 2.11−2.04 (m, 1H), 1.58−1.20 (m, 10H), 0.88 (t, J = 6.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.2, 145.2, 136.1, 134.8, 133.9, 131.9, 131.7, 130.8, 130.0, 129.9, 129.4, 127.1, 126.5, 124.4, 124.3, 123.4, 123.2, 120.4, 114.3, 72.9, 63.5, 50.6, 44.8, 38.3, 36.4, 35.7, 32.3, 31.8, 22.5, 21.5, 14.0. MS (ESI) m/z 652 $[M + H]^+$; HRMS: Exact mass calcd for $C_{33}H_{38}O_7N_3S_2$ $[M + H]^+$: 652.2145. Found: 652.2155.

*2′-((2-Nitrophenyl)sulfonyl)-2-(thiophen-2-yl)-9′-tosyl-1′,2,2′,3,3′,5,6,9′-octahydrospiro[pyran-4,4′-pyrido[3,4-b]indole] (**8e**, Table 2; entry e).* 0.0907 g, yield 78%; white solid, mp 185 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.18−8.08 (m, 2H), 7.83−7.66 (m, 6H), 7.35−7.20 (m, 5H), 6.96−6.9 (m, 2H), 4.94 (dd, J = 1.7, 11.8 Hz, 1H), 4.84 (s, 2H), 4.12 (dd, J = 5.0, 12.4 Hz, 1H), 4.04−3.77 (m, 3H), 2.68−2.46 (m, 2H), 2.35 (s, 3H), 2.0 (d, J = 14.1 Hz, 1H), 1.67−1.61 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.2, 145.3, 145.1, 136.1, 134.8, 134.0, 132.0, 131.7, 130.8, 130.1, 129.6, 126.9, 126.5, 126.4, 124.5, 124.3, 123.5, 123.4, 122.8, 120.4, 114.4, 71.1, 64.1, 50.3, 44.8, 39.9, 36.0, 31.8, 21.5. MS (ESI) m/z 686 $[M + Na]^+$; HRMS: Exact mass calcd for $C_{32}H_{29}O_7N_3NaS_3$ $[M + Na]^+$: 686.1059. Found: 686.1076.

*2′-((2-Nitrophenyl)sulfonyl)-2-(m-tolyl)-9′-tosyl-1′,2,2′,3,3′,5,6,9′-octahydrospiro[pyran-4,4′-pyrido[3,4-b]indole] (**8f**, Table 2, entry f).* 0.095 g, yield 81%, white solid, mp 172 °C, ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.18−8.14 (m, 1H), 8.10 (d, J = 8.0 Hz, 1H), 7.82−7.68 (m, 5H), 7.32−7.14 (m, 8H), 7.05 (d, J = 7.1 Hz, 1H), 4.90 (d, J = 16.6 Hz, 1H), 4.78 (d, J = 16.6 Hz, 1H), 4.68 (dd, J = 1.6, 11.7 Hz, 1H), 4.15 (dd, J = 4.5, 12.3 Hz, 1H), 4.04 (d, J = 12.2 Hz, 1H), 3.95 (d, J = 1.6, 12.5 Hz, 1H), 3.75 (d, J = 13.2 Hz, 1H), 2.65 (td, J = 5.3, 13.8 Hz, 1H), 2.37−2.30 (m, 7H), 1.89 (d, J = 14.3 Hz, 1H), 1.60 (d, J = 14.3 Hz, 1H). ^{13}C NMR

DOI: 10.1021/acs.joc.5b01108
J. Org. Chem. 2015, 80, 8807−8814

(75 MHz, $CDCl_3$): δ 147.9, 145.1, 141.7, 137.5, 135.8, 134.4, 133.8, 131.8, 131.3, 130.3, 129.8, 129.3, 127.8, 126.7, 126.1, 125.8, 124.2, 124.1, 123.1, 122.9, 122.3, 120.1, 114.0, 74.7, 63.7, 50.0, 44.6, 35.8, 31.7, 21.2, 21.1. MS (ESI) *m/z* 672 $[M + H]^+$; HRMS: Exact mass calcd for $C_{35}H_{34}O_7N_3S_2$ $[M + H]^+$: 672.1832. Found: 672.1839.

2-(3-Fluorophenyl)-2′-((2-nitrophenyl)sulfonyl)-9′-tosyl-1′,2,2′,3,3′,5,6,9′-octahydrospiro[pyran-4,4′-pyrido[3,4-b]indole] (**8g**, Table 2, entry g). 0.098 g, yield 83%, white solid, mp 150 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.11−8.13 (m, 1H), 8.09 (d, *J* = 7.5 Hz, 1H), 7.86−7.66 (m, 6H), 7.35−7.20 (m, 5H), 7.17−7.08 (m, 2H), 6.97−6.87 (m, 1H), 5.04−4.86 (m, 1H), 4.82−4.67 (m, 2H), 4.25−4.05 (m, 2H), 4.02−3.86 (m, 1H), 3.63 (d, *J* = 13.4 Hz, 1H), 2.68 (td, *J* = 5.8, 14.3 Hz, 1H), 2.47−2.17 (m, 4H), 1.95 (d, *J* = 14.1 Hz, 1H), 1.69−1.65 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.7, 161.7, 148.2, 145.3, 144.8, 144.8, 136.1, 134.7, 134.0, 132.0, 131.8, 130.7, 130.0, 129.7, 129.6, 126.9, 126.4, 124.5, 124.3, 123.3, 122.9, 121.5, 120.2, 114.3, 114.1, 113.9, 112.5, 112.3, 74.3, 63.9, 50.3, 44.9, 40.1, 36.1, 32.0, 21.5. MS (ESI) *m/z* 676 $[M + H]^+$; HRMS: Exact mass calcd for $C_{34}H_{31}O_7N_3FS_2$ $[M + H]^+$: 676.1582. Found: 676.1588.

2-(3-Chlorophenyl)-2′-((2-nitrophenyl)sulfonyl)-9′-tosyl-1′,2,2′,3,3′,5,6,9′-octahydrospiro[pyran-4,4′-pyrido[3,4-b]indole] (**8h**, Table 2, entry h). 0.097 g, yield 80%, white solid, mp 170 °C, ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.18−8.15 (m, 1H), 8.10 (d, *J* = 8.2 Hz, 1H), 7.83−7.79 (m, 2H), 7.75−7.68 (m, 4H), 7.40−7.37 (m, 1H), 7.32−7.19 (m, 7H), 4.99−4.90 (m, 1H), 4.77−4.68 (m, 2H), 4.20−4.07 (m, 2H), 3.94 (td, *J* = 1.9, 12.6 Hz, 1H), 3.62 (d, *J* = 13.4 Hz, 1H), 2.68 (td, *J* = 5.4, 13.7 Hz, 1H), 2.37−2.28 (m, 4H), 2.26−2.18 (m, 1H), 1.96−1.91 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.2, 145.3, 144.2, 136.1, 134.8, 134.1, 134.0, 132.0, 131.8, 130.8, 130.1, 129.6, 129.5, 127.4, 126.9, 126.4, 125.6, 124.5, 124.3, 123.8, 123.4, 122.9, 120.3, 114.4, 74.3, 64.0, 50.3, 44.9, 40.1, 36.1, 32.1, 21.5. MS (ESI) *m/z* 692 $[M + H]^+$; HRMS: Exact mass calcd for $C_{34}H_{31}O_7N_3ClS_2$ $[M + H]^+$: 692.1286. Found: 692.1291.

2-Cyclohexylspiro-2′-((2-nitrophenyl)sulfonyl)-9′-tosyl-1′,2,2′,3,3′,5,6,9′-octahydrospiro[pyran-4,4′-pyrido[3,4-b]indole] (**8i**, Table 2, entry (i). 0.085 g, yield 75%, white solid, mp 195 °C, ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.13−8.07 (m, 2H), 7.82−7.67 (m, 6H), 7.34−7.21 (m, 4H), 4.96 (d, *J* = 16.4 Hz, 1H), 4.55 (d, *J* = 16.4 Hz, 1H), 4.18 (d, *J* = 13.1 Hz, 1H), 3.86 (td, *J* = 2.1, 12.5 Hz, 1H), 3.79−3.73 (m, 1H), 3.35 (d, *J* = 13.1 Hz, 1H), 2.37−2.25 (m, 5H), 1.75−1.20 (m, 13H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.4, 145.2, 136.2, 134.9, 133.9, 131.8, 131.5, 130.8, 130.1, 129.6, 127.0, 126.5, 124.4, 124.2, 123.9, 123.2, 120.6, 114.4, 112.9, 71.5, 60.3, 56.7, 53.1, 44.6, 42.1, 41.5, 35.6, 32.9, 31.3, 25.6, 21.8, 21.5. MS (ESI) *m/z* 650 $[M + H]^+$; HRMS: Exact mass calcd for $C_{33}H_{36}O_7N_3S_2$ $[M + H]^+$: 650. 1989. Found: 650. 2007.

2-(o-Tolyl)-2′,9′-ditosyl-1′,2,2′,3,3′,5,6,9′-octahydrospiro[pyran-4,4′-pyrido[3,4-b]indole] (**8j**, Table 2, entry j). 0.0939 g, yield 79%, white solid, mp 182 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.08 (d, *J* = 7.1 Hz, 1H), 7.85 (d, *J* = 8.1 Hz, 2H), 7.74 (d, *J* = 7.5 Hz, 1H), 7.65 (d, *J* = 8.3 Hz, 2H), 7.52 (d, *J* = 7.5 Hz, 1H), 7.42 (d, *J* = 8.1 Hz, 1H), 7.32−7.07 (m, 8H), 4.89 (d, *J* = 10.9 Hz, 1H), 4.69 (d, *J* = 16.2 Hz, 1H), 4.41 (d, *J* = 16.2 Hz, 1H), 4.16 (dd, *J* = 4.9, 12.2 Hz, 1H), 4.0−3.8 (m, 2H), 3.29 (d, *J* = 12.0 Hz, 1H), 2.75−2.60 (m, 1H), 2.48 (s, 3H), 2.40 (s, 3H), 2.33 (s, 3H), 2.31−2.20 (m, 1H), 1.90 (d, *J* = 13.9 Hz, 1H), 1.57 (d, *J* = 13.9 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.2, 144.0, 140.2, 136.2, 135.0, 134.4, 133.5, 130.2, 130.0, 130.01, 129.9, 127.5, 127.2, 126.9, 126.3, 126.1, 125.1, 124.3, 123.2, 122.9, 120.2, 114.3, 72.2, 64.2, 50.3, 45.3, 38.9, 36.1, 32.3, 21.5, 21.5, 19.0. MS (ESI) *m/z* 641 $[M + H]^+$; HRMS: Exact mass calcd for $C_{36}H_{37}O_5N_2S_2$ $[M + H]^+$: 641.2138. Found: 641.2143.

2-(2-Chlorophenyl)-2′,9′-ditosyl-1′,2,2′,3,3′,5,6,9′-octahydrospiro[pyran-4,4′-pyrido[3,4-b]indole] (**8k**, Table 2, entry k). 0.092 g, yield 75%, white solid, mp 128 °C, ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07 (d, *J* = 8.2 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 2H), 7.70−7.60 (m, 4H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.33−7.16 (m, 7H), 5.01 (d, *J* = 10.9 Hz, 1H), 4.79 (d, *J* = 16.1 Hz, 1H), 4.34 (d, *J* = 16.1 Hz, 1H), 4.18 (dd, *J* = 5.1, 12.3 Hz, 1H), 4.03 (d, *J* = 12.5 Hz, 2H), 3.12 (d, *J* = 12.0 Hz, 1H), 2.49 (s, 3H), 2.47−2.42 (m, 1H), 2.34 (s, 3H), 2.32−2.25 (m, 1H), 1.90 (d, *J* = 14.0 Hz, 1H), 1.78 (d, *J* = 14.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.2, 144.0, 139.8, 136.2, 135.0, 133.6, 131.8, 130.0, 129.1, 128.4, 127.6, 127.1, 126.9, 126.8, 126.4, 124.3, 123.2, 122.7, 120.1, 114.4, 72.1, 64.4, 49.9, 45.2, 39.3, 36.2, 31.6, 21.5. MS (ESI) *m/z* 661 $[M + H]^+$; HRMS: Exact mass calcd for $C_{35}H_{34}O_5N_2ClS_2$ $[M + H]^+$: 661.1592. Found: 661.1595.

2-(4-Methoxyphenyl)-2′,9′-ditosyl-1′,2,2′,3,3′,5,6,9′-octahydrospiro[pyran-4,4′-pyrido[3,4-b]indole] (**8l**, Table 2, entry l). 0.103 g, yield 85%, white solid, mp 195 °C, ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09 (d, *J* = 8.08 Hz, 1H), 7.86−7.82 (m, 2H), 7.73 (d, *J* = 7.7 Hz, 1H), 7.68 (m, 2H), 7.42 (d, *J* = 7.9 Hz, 2H), 7.32−7.27 (m, 3H), 7.25−7.20 (m, 3H), 6.87−6.83 (m, 2H), 4.68−4.60 (m, 2H), 4.57 (d, *J* = 16.1 Hz, 1H), 4.13 (dd, *J* = 4.5, 12.2 Hz, 1H), 3.92 (td, *J* = 1.8, 12.5 Hz, 1H), 3.78 (s, 3H), 3.68 (d, *J* = 12.3 Hz, 1H), 3.42 (d, *J* = 12.3 Hz, 1H), 2.60 (dd, *J* = 5.3, 13.5 Hz, 1H), 2.48 (s, 3H), 2.36−2.29 (m, 4H), 1.85 (d, *J* = 14.2 Hz, 1H), 1.61−1.60 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.9, 145.2, 143.9, 136.2, 135.0, 134.3, 134.0, 130.0, 127.4, 127.0, 126.9, 126.3, 124.3, 123.2, 123.0, 120.2, 114.3, 113.6, 74.7, 64.1, 55.2, 50.2, 45.2, 40.1, 36.1, 32.0, 21.5. MS (ESI) *m/z* 657 $[M + H]^+$; HRMS: Exact mass calcd for $C_{36}H_{37}O_6N_2S_2$ $[M + H]^+$: 657.2087. Found: 657.2091.

2-Isobutyl-2′,9′-ditosyl-1′,2,2′,3,3′,5,6,9′-octahydrospiro[pyran-4,4′-pyrido[3,4-b]indole] (**8m**, Table 2, entry m). 0.071 g, yield 63%, white solid, mp 90 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.08 (d, *J* = 8.1 Hz, 1H), 7.81 (d, *J* = 8.1 Hz, 1H), 7.74−7.64 (m, 3H), 7.41 (d, *J* = 8.1 Hz, 1H), 7.32−7.18 (m, 5H), 4.55 (d, *J* = 4.9 Hz, 2H), 3.96 (dd, *J* = 5.0, 12.0 Hz, 1H), 3.76−3.56 (m, 2H), 3.42 (ABq, *J* = 12.0 Hz, 2H), 2.51−2.38 (m, 4H), 2.36 (s, 3H), 2.09−1.96 (m, 1H), 1.77 (p, *J* = 6.2, 13.4 Hz, 1H), 1.65−1.44 (m, 2H), 1.35−1.08 (m, 2H), 1.75−1.02 (m, 7H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.2, 143.9, 136.2, 135.1, 133.8, 130.0, 129.9, 129.9, 127.5, 127.0, 126.4, 124.3, 123.3, 123.2, 120.4, 114.3, 71.2, 63.6, 50.5, 45.6, 45.2, 38.7, 35.7, 32.4, 24.3, 23.0, 22.5, 21.5. MS (ESI) *m/z* 607 $[M + H]^+$; HRMS: Exact mass calcd for $C_{33}H_{39}O_5N_2S_2$ $[M + H]^+$: 607.2294. Found: 607.2302.

2′,9′-Ditosyl-2-(2,6,6-trimethylcyclohex-1-en-1-yl)-1′,2,2′,3,3′,5,6,9′-octahydrospiro[pyran-4,4′-pyrido[3,4-b]indole] (**8n**, Table 2, entry n). 0.097 g, yield 78%, white solid, mp 98 °C, ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.08 (d, *J* = 8.0 Hz, 1H), 7.85−7.81 (m, 2H), 7.71−7.65 (m, 3H), 7.42 (d, *J* = 8.0 Hz, 2H), 7.31−7.01 (m, 4H), 5.3 (s, 1H), 4.51 (ABq, *J* = 16.0 Hz, 2H), 4.24 (dd, *J* = 4.7, 12.2 Hz, 1H), 3.78 (t, *J* = 12.5 Hz, 1H), 3.57 (d, *J* = 12.0 Hz, 1H), 3.41 (d, *J* = 12.0 Hz, 1H), 2.71−2.63 (m, 1H), 2.54 (dd, *J* = 5.3, 13.7 Hz, 1H), 2.48 (s, 3H), 2.35 (s, 3H), 2.03 (s, 3H), 1.99−1.84 (m, 2H), 1.63−1.23 (m, 6H), 1.17 (s, 3H), 0.97 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.1, 143.9, 137.2, 136.2, 133.3, 132.1, 130.0, 129.9, 129.7, 127.6, 127, 126.4, 124.2, 123.2, 120.0, 114.3, 72.5, 64.1, 50.1, 45.3, 39.7, 36.7, 36.2, 34.5, 34, 32.2, 28.6, 28.2, 27.9, 21.5, 19.1. MS (ESI) *m/z* 673 $[M + H]^+$; HRMS: Exact mass calcd for $C_{38}H_{45}O_5N_2S_2$ $[M + H]^+$: 673.2764. Found: 673.2770.

2-(4-Nitrophenyl)-2′,9′-ditosyl-1′,2,2′,3,3′,5,6,9′-octahydrospiro-[pyran-4,4′-pyrido[3,4-b]indole] (**8o**, Table 2, entry o). 0.08 g, yield 64%, white solid, mp 93 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.18 (d, *J* = 8.4 Hz, 2H), 8.08 (d, *J* = 8.1 Hz, 1H), 7.85 (d, *J* = 8.1 Hz, 1H), 7.72−7.65 (m, 3H), 7.59−7.54 (m, 1H), 7.44 (d, *J* = 8.1 Hz, 2H), 7.34−7.16 (m, 5H), 4.91−4.78 (m, 2H), 4.43 (d, *J* = 16 Hz, 2H), 4.18 (dd, *J* = 4.7, 12.0 Hz, 1H), 4.10−3.73 (m, 2H), 3.13 (d, *J* = 12.4 Hz, 1H), 2.72 (td, *J* = 5.6, 13.9 Hz, 1H), 2.49 (s, 3H), 2.33 (s, 3H), 2.08 (t, *J* = 10.0 Hz, 2H), 1.60 (d, *J* = 7.7 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.6, 147.0, 145.3, 144.1, 136.1, 135.0, 134.1, 130.2, 130.1, 129.8, 129.8, 129.7, 129.6, 127.8, 127.3, 127.1, 126.8, 126.4, 126.2, 124.4, 123.5, 123.4, 123.3, 122.4, 120.0, 114.4, 74.2, 64.0, 50.0, 45.3, 40.1, 36.1, 32.0, 21.5. MS (ESI) *m/z* 672 $[M + H]^+$; HRMS: Exact mass calcd for $C_{35}H_{34}O_7N_3S_2$ $[M + H]^+$: 672.1832. Found: 672.1841.

2-((E)-Styryl)-2′,9′-ditosyl-1′,2,2′,3,3′,5,6,9′-octahydrospiro-[pyran-4,4′-pyrido[3,4-b]indole] (**8p**, Table 2, entry p). 0.094 g, yield 78%, white solid, mp 125 °C, ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10 (d, *J* = 8.2 Hz, 1H), 7.85−7.82 (m, 2H), 7.74 (d, *J* = 7.9 Hz, 1H), 7.69−7.67 (m, 2H), 7.42 (d, *J* = 7.9 Hz, 2H), 7.37−7.34 (m, 2H), 7.31−7.25 (m, 3H), 7.25−7.21 (m, 4H), 6.63 (d, *J* = 16.0 Hz, 1H), 6.17 (dd, *J* = 5.4, 16.0 Hz, 1H), 4.59 (ABq, *J* = 16.1 Hz, 2H), 4.29 (dd, *J* = 5.4, 11.2 Hz, 2H), 4.07 (dd, *J* = 4.5, 12.2 Hz, 1H), 3.85 (td, *J* = 1.9, 12.6 Hz, 1H), 3.49 (ABq, *J* = 12.2 Hz, 1H), 2.56−2.46 (m, 4 H), 2.35 (s, 3H), 2.29−2.21 (m, 1H), 1.76 (d, *J* = 14.0 Hz, 1H), 1.58−1.55 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.2, 144.0, 136.5, 136.2, 135.0, 133.8, 130.4, 130.0, 130.0, 129.4, 128.4, 127.5, 127.4, 126.9, 126.4, 126.3, 124.3, 123.2, 122.9, 120.3, 114.3, 73.2, 63.6, 50.2, 45.2, 38.3, 35.7, 32.0, 21.5. MS (ESI) *m/z*

DOI: 10.1021/acs.joc.5b01108
J. Org. Chem. 2015, 80, 8807−8814

653 [M + H]$^+$; HRMS: Exact mass calcd for $C_{37}H_{37}O_5N_2S_2$ [M + H]$^+$: 653.2138. Found: 653.2146.

2-(Naphthalen-1-yl)-2′-((2-nitrophenyl)sulfonyl)-9′-tosyl-1′,2,2′,3,3′,5,6,9′-octahydrospiro[pyran-4,4′-pyrido[3,4-b]indole] (**8q**, Table 2, entry q). 0.103 g, yield 83%, white solid, m.p.148 °C, ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.23 (d, J = 8.5 Hz, 1H), 8.21−8.16 (m, 1H), 8.09 (d, J = 7.9 Hz, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.79−7.66 (m, 7H), 7.57−7.51 (m, 1H), 7.48−7.42 (m, 2H), 7.31−7.18 (m, 5H), 5.44 (d, J = 10.3 Hz, 1H), 4.84 (ABq, J = 16.6 Hz, 2H), 4.26 (dd, J = 4.5, 12.3 Hz, 1H), 4.19 (d, J = 13.1 Hz, 1H), 4.12 (td, J = 1.8, 12.6 Hz, 1H), 3.88 (d, J = 13.1 Hz, 1H), 2.74 (td, J = 5.4, 13.7 Hz, 1H), 2.56−2.47 (m, 1H), 2.30 (s, 3H), 2.09 (d, J = 14.3 Hz, 1H), 1.70 (d, J = 14.3 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.4, 145.3, 137.8, 136.2, 134.8, 134.0, 133.5, 131.9, 131.3, 130.9, 130.1, 129.5, 128.6, 127.9, 127.0, 126.4, 126.1, 125.4, 125.3, 124.5, 124.3, 123.3, 123.1, 122.8, 120.3, 114.4, 72.2, 64.4, 50.6, 44.9, 39.4, 36.4, 32.4, 21.5. MS (ESI) m/z 708 [M + H]$^+$; HRMS: Exact mass calcd for $C_{38}H_{34}O_7N_3S_2$ [M + H]$^+$: 708.1832. Found: 708.1843.

6′-Chloro-2-(4-methoxyphenyl)-2′,9′-ditosyl-1′,2,2′,3,3′,5,6,9′-octahydrospiro[pyran-4,4′-pyrido[3,4-b]indole] (**8r**, Table 2, entry r). 0.102 g, yield 82%, white solid, mp 160 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.01 (d, J = 8.9 Hz, 1H), 7.85−7.81 (m, 2H), 7.68 (d, J = 1.9 Hz, 1H), 7.65−7.62 (m, 2H), 7.42 (d, J = 8.0 Hz, 2H), 7.32−7.29 (m, 2H), 7.25−7.22 (m, 3H), 6.88−6.85 (m, 2H), 4.70−4.59 (m, 2H), 4.50 (d, J = 16.3 Hz, 1H), 4.14 (dd, J = 4.6, 12.2 Hz, 1H), 3.95−3.85 (m, 1H), 3.78 (s, 3H), 3.73 (d, J = 12.3 Hz, 1H), 3.35 (d, J = 12.3 Hz, 1H), 2.54 (dd, J = 5.3, 13.5 Hz, 1H), 2.48 (s, 3H), 2.35 (s, 3H), 2.25−2.16 (m, 1H), 1.87 (d, J = 14.0 Hz, 1H), 1.59−1.57 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.0, 145.5, 144.1, 134.7, 134.5, 134.1, 133.9, 131.5, 130.2, 130.0, 129.1, 128.2, 127.4, 126.9, 126.3, 124.5, 122.5, 119.9, 115.3, 113.7, 74.7, 64.0, 55.2, 50.1, 45.2, 40.1, 36.1, 32.0, 21.5. MS (ESI) m/z 713 [M + H]$^+$; HRMS: Exact mass calcd for $C_{36}H_{35}O_6N_2ClNaS_2$ [M + Na]$^+$: 713.1516. Found: 713.1519.

6′-Chloro-2-(thiophen-2-yl)-2′,9′-ditosyl-1′,2,2′,3,3′,5,6,9′-octahydrospiro[pyran-4,4′-pyrido[3,4-b]indole] (**8s**, Table 2, entry s). 0.093 g, yield 80%, white solid, mp 140−142 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.03 (d, J = 8.8 Hz, 1H), 7.82 (d, J = 8.1 Hz, 2H), 7.71−7.63 (m, 3H), 7.41 (d, J = 7.9 Hz, 2H), 7.28−7.22 (m, 4H), 6.97−6.94 (m, 2H), 4.90 (dd, J = 1.7, 11.3 Hz, 1H), 4.61−4.56 (m, 2H), 4.13 (dd, J = 4.9, 12.0 Hz, 1H), 3.99−3.87 (m, 1H), 3.51 (ABq, J = 12.2 Hz, 2H), 2.55−2.31 (m, 8H), 2.0 (d, J = 13.7 Hz, 1H), 1.60 (d, J = 13.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.6, 145.0, 144.1, 134.8, 134.6, 133.8, 131.7, 130.2, 130.1, 129.3, 128.2, 127.5, 126.4, 124.7, 124.6, 123.5, 122.2, 119.9, 115.4, 71.1, 64.1, 50.1, 45.2, 39.8, 36.0, 31.9, 29.6, 21.6, 21.5. MS (ESI) m/z 667 [M + H]$^+$; HRMS: Exact mass calcd for $C_{33}H_{32}O_5N_2ClS_3$ [M + H]$^+$: 667.1156. Found: 667.1159.

6′-Chloro-2′,9′-ditosyl-2-(3,4,5-trimethoxyphenyl)-1′,2,2′,3,3′,5,6,9′-octahydrospiro[pyran-4,4′-pyrido[3,4-b]indole] (**8t**, Table 2, entry t). 0.115 g, yield 88%, white solid, mp 115 °C, ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01 (d, J = 8.8 Hz, 1H), 7.86−7.83 (m, 2H), 7.69 (d, J = 1.9 Hz, 1H), 7.66−7.64 (m, 2H), 7.45−7.41 (d, J = 8.0 Hz, 2H), 7.26−7.23 (m, 3H), 6.63 (s, 2H), 4.70 (d, J = 16.4 Hz, 1H), 4.64 (dd, J = 1.8, 11.5 Hz, 1H), 4.50 (d, J = 16.4 Hz, 1H), 4.17 (dd, J = 4.5, 12.2 Hz, 1H), 3.93−3.86 (m, 8H), 3.81 (s, 3H), 3.33 (d, J = 12.3 Hz, 1H), 2.55 (td, J = 5.3, 13.7 Hz, 1H), 2.49 (s, 3H), 2.36 (s, 3H), 2.24−2.17 (m, 1H), 1.93 (d, J = 14.1 Hz, 1H), 1.60−1.58 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.2, 145.6, 144.1, 137.7, 137.2, 134.7, 134.5, 134.0, 134.0, 131.6, 131.1, 130.2, 130.0, 129.5, 129.1, 128.3, 128.2, 127.4, 126.4, 124.5, 122.3, 119.9, 116.6, 116.2, 115.4, 102.5, 75.2, 64.0, 60.7, 56.1, 50.1, 45.2, 40.2, 36.1, 32.0, 21.5. MS (ESI) m/z 751 [M + H]$^+$; HRMS: Exact mass calcd for $C_{38}H_{40}O_8N_2ClS_2$ [M + H]$^+$: 751.1909. Found: 751.1903.

6′-Chloro-2-(3,4-dimethoxyphenyl)-2′,9′-ditosyl-1′,2,2′,3,3′,5,6,9′-octahydrospiro[pyran-4,4′-pyrido[3,4-b]indole] (**8u**, Table 2, entry u). 0.108 g, yield 86%, white solid, mp 125 °C, ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.02 (d, J = 9.0 Hz, 1H), 7.86−7.82 (m, 2H), 7.70 (d, J = 1.8 Hz, 1H), 7.66−7.63 (m, 2H), 7.42 (d, J = 8.2 Hz, 2H), 7.26−7.22 (m, 3H), 6.98 (d, J = 1.6 Hz, 1H), 6.90 (dd, J = 1.6, 8.2 Hz, 1H), 6.82 (d, J = 8.3 Hz, 1H), 4.65 (d, J = 16.4 Hz, 2H), 4.52 (d, J = 16.3 Hz, 1H), 4.16 (dd, J = 4.7, 12.2 Hz, 1H), 3.89 (m, 7H), 3.73 (d, J = 12.3 Hz, 1H), 3.37 (d, J = 12.3 Hz, 1H), 2.55 (dd, J = 5.3, 13.7 Hz, 1H), 2.48 (s, 3H), 2.35 (s, 3H), 2.27−2.19 (m, 1H), 1.89 (d, J = 14.0 Hz, 1H), 1.58 (d, J = 14.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.9, 148.3, 145.6, 144.0, 134.7, 134.6, 134.5, 133.9, 131.6, 130.2, 130.0, 129.1, 128.2, 127.4, 126.3, 124.5, 122.4, 119.9, 117.8, 115.3, 110.9, 108.9, 74.8, 64.0, 55.9, 55.8, 50.1, 45.2, 40.1, 36.1, 32.0. MS (ESI) m/z 738 [M + NH$_4$]$^+$; HRMS: Exact mass calcd for $C_{37}H_{41}O_7N_3ClS_2$ [M + NH$_4$]$^+$: 738.20690. Found: 738.20694.

(2S,4S)-2-(4-Bromophenyl)-6′-methyl-2′,9′-ditosyl-1′,2,2′,3,3′,5,6,9′-octahydrospiro[pyran-4,4′-pyrido[3,4-b]indole] (**8v**, Table 2, entry w). 0.0975 g, yield 75%, white solid, mp 194 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, J = 8.5 Hz, 1H), 7.84 (d, = 8.3 Hz, 2H), 7.64 (d, J = 8.4 Hz, 2H), 7.47−7.39 (m, 5H), 7.30−7.25 (m, 2H), 7.21 (d, J = 8.0 Hz, 2H), 7.09 (d, J = 8.5 Hz, 1H), 4.74 (d, J = 16.2 Hz, 1H), 4.67 (dd, J = 1.5, 11.3 Hz, 1H), 4.44 (d, J = 16.2 Hz, 1H), 4.16 (dd, J = 4.7, 12.2 Hz, 1H), 3.95−3.80 (m, 2H), 3.23 (d, J = 12.3 Hz, 1H), 2.65 (td, J = 5.3, 13.7 Hz, 1H), 2.48 (s, 3H), 2.41 (s, 3H), 2.33 (s, 3H), 2.19 (t, J = 11.9 Hz, 1H), 1.93 (d, J = 14.0 Hz, 1H), 1.56−1.50 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.1, 144.0, 141.2, 135.0, 134.4, 134.1, 132.9, 131.3, 130.1, 130.0, 127.4, 127.3, 127.1, 126.4, 125.7, 122.6, 121.1, 120.1, 114.1, 74.4, 64.1, 50.2, 45.3, 40.1, 36.1, 32.0, 21.5, 21.4. MS (ESI) m/z 719 [M + H]$^+$; HRMS: Exact mass calcd for $C_{36}H_{36}O_5N_2BrS_2$ [M + H]$^+$: 719.1244. Found: 719.1249.

(2S,4S)-2-(4-Bromophenyl)-7′-methyl-2′,9′-ditosyl-1′,2,2′,3,3′,5,6,9′-octahydrospiro[pyran-4,4′-pyrido[3,4-b]indole] (**8w**, Table 2, entry w). 0.0975 g, yield 75%, white solid, mp 182 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (s, 1H), 7.83 (d, J = 8.2 Hz, 2H), 7.64 (d, J = 8.2 Hz, 2H), 7.55 (d, J = 8.0 Hz, 1H), 7.346−7.39 (m, 4H), 7.28−7.21 (m, 4H), 7.05 (d, J = 7.6 Hz, 1H), 4.70 (d, J = 16.2 Hz, 1H), 4.66 (dd, J = 1.5, 11.3 Hz, 1H), 4.44 (d, J = 16.2 Hz, 1H), 4.13 (dd, J = 4.7, 12.2 Hz, 1H), 3.89 (dt, J = 1.5, 11.3 Hz, 1H), 3.79 (d, J = 12.3 Hz, 1H), 3.26 (d, J = 12.3 Hz, 1H), 2.61 (dt, J = 5.3, 13.7 Hz, 1H), 2.48 (s, 3H), 2.45 (s, 3H), 2.33 (s, 3H), 2.18 (t, J = 11.9 Hz, 1H), 1.91 (d, J = 14.0 Hz, 1H), 1.54 (d, J = 14.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.1, 144.0, 141.3, 136.6, 135.2, 134.6, 134.0, 131.3, 130.1, 130.0, 129.3, 127.4, 127.3, 126.3, 124.7, 124.6, 122.7, 121.1, 119.7, 114.5, 78.4, 64.1, 50.1, 45.3, 40.2, 36.0, 34.0, 32.4, 22.3, 21.8, 14.0. MS (ESI) m/z 719 [M + H]$^+$; HRMS: Exact mass calcd for $C_{36}H_{36}O_5N_2BrS_2$ [M + H]$^+$: 719.1244. Found: 719.1249.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01108.

Copies of ^{1}H and ^{13}C NMR spectra of **8a**−**w** and X-ray crystallography (**8a**) (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: basireddy@iict.res.in. Fax: 91-40-27160512.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

M.R.R. and C.R.R. thank CSIR and S.Y. and G.R.K. thank UGC, New Delhi, for the award of fellowships. B.V.S.R. thanks CSIR, New Delhi, for the financial support as a part of the XII five year plan program under title ORIGIN (CSC-0108).

■ REFERENCES

(1) Cao, R.; Peng, W.; Wang, Z.; Xu, A. *Curr. Med. Chem.* **2007**, *14*, 479.

(2) (a) Herraiz, T. J. *J. Agric. Food Chem.* **2000**, *48*, 4900. (b) Buckholtz, N. S. *Life Sci.* **1980**, *27*, 893. (c) Herraiz, T.; Galisteo, J. *J. Agric. Food Chem.* **2003**, *51*, 7156.

(3) (a) Stöckigt, J.; Antonchick, A. P.; Wu, F.; Waldmann, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 8538. (b) Larghi, E. L.; Amongero, M.; Bracca,

DOI: 10.1021/acs.joc.5b01108
J. Org. Chem. 2015, 80, 8807−8814

A. B. J.; Kaufman, T. S. *ARKIVOC* **2005**, *2005* (12), 98. (c) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797. (d) Kusurkar, R. S.; Goswami, S. K.; Vyas, S. M. *Tetrahedron Lett.* **2003**, *44*, 4761. (e) Pachter, I. J.; Mohrbacher, R. J.; Zacharias, D. E. *J. Am. Chem. Soc.* **1961**, *83*, 635.

(4) (a) Lesma, G.; Cecchi, R.; Cagnotto, A.; Gobbi, M.; Meneghetti, F.; Musolino, M.; Sacchetti, A.; Silvani, A. *J. Org. Chem.* **2013**, *78*, 2600. (b) Zou, B.; Chan, W. L.; Ding, M.; Leong, S. Y.; Nilar, S.; Seah, P. G.; Liu, W.; Karuna, R.; Blasco, F.; Yip, A.; Chao, A.; Susila, A.; Dong, H.; Wang, Q. Y.; Xu, H. Y.; Chan, K.; Wan, K. F.; Gu, F.; Diagana, T. T.; Wagner, T.; Dix, I.; Shi, P. Y.; Smith, P. W. *ACS Med. Chem. Lett.* **2015**, *6*, 344.

(5) Rottmann, M.; McNamara, C.; Yeung, B. K. S.; Lee, M. C. S.; Zou, B.; Russell, B.; Seitz, P.; Plouffe, D. M.; Dharia, N. V.; Tan, J.; Cohen, S. B.; Spencer, K. R.; González-Páez, G. E.; Lakshminarayana, S. B.; Goh, A.; Suwanarusk, R.; Jegla, T.; Schmitt, E. K.; Beck, H.-P.; Brun, R.; Nosten, F.; Renia, L.; Dartois, V.; Keller, T. H.; Fidock, D. A.; Winzeler, E. A.; Diagana, T. T. *Science* **2010**, *329*, 1175.

(6) (a) Yang, Y.-F.; Li, L.-H.; He, Y.-T.; Luo, J.-Y.; Liang, Y.-M. *Tetrahedron* **2014**, *70*, 702. (b) Wang, S. G.; Zhang, W.; You, S. L. *Org. Lett.* **2013**, *15*, 1488.

(7) (a) Shimada, T.; Nakamura, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 10546. (b) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Org. Lett.* **2004**, *6*, 3199. (c) Hiroya, K.; Itoh, S.; Sakamoto, T. *J. Org. Chem.* **2004**, *69*, 1126. (d) Grimster, N. P.; Gauntlett, C.; Godfrey, C. R. A.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 3125. (e) Li, X.; Chianese, A. R.; Vogel, T.; Crabtree, R. H. *Org. Lett.* **2005**, *7*, 5437. (f) Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 4972. (g) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172. (h) Subba Reddy, B. V.; Swain, M.; Madhusudana Reddy, S.; Yadav, J. S.; Sridhar, B. *J. Org. Chem.* **2012**, *77*, 11355.

(8) (a) Rudolph, M.; Hashmi, A. S. K. *Chem. Soc. Rev.* **2012**, *41*, 2448. (b) Gorin, D. J.; Toste, D. *Nature* **2007**, *446*, 395. (c) Stephen, A.; Hashmi, K. *Chem. Rev.* **2007**, *107*, 3180. (d) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (e) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266. (f) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326. (g) Gorin, D.; Sherry, B.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351. (h) Marion, N.; Nolan, S. *Chem. Soc. Rev.* **2008**, *37*, 1776. (i) Hashmi, A. S. K.; Rudolph, M. *Chem. Soc. Rev.* **2008**, *37*, 1766.

(9) (a) Zhang, Y.; Donahue, J. P.; Li, C. J. *Org. Lett.* **2007**, *9*, 627. (b) Arcadi, A.; Bianchi, G.; Chiarini, M.; D'Anniballe, G.; Marinelli, F. *Synlett* **2004**, 944. (c) Arcadi, A.; Alfonsi, M.; Bianchi, G.; D'Anniballe, G.; Marinelli, F. *Adv. Synth. Catal.* **2006**, *348*, 331. (d) Alfonsi, M.; Arcadi, A.; Aschi, M.; Bianchi, G.; Marinelli, F. *J. Org. Chem.* **2005**, *70*, 2265.

(10) Lee, J. M.; Na, Y.; Han, H.; Chang, S. *Chem. Soc. Rev.* **2004**, *33*, 302.

(11) CCDC 1056270 contains supplementary crystallographic data for product **8a**. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html.

DOI: 10.1021/acs.joc.5b01108
J. Org. Chem. 2015, 80, 8807−8814