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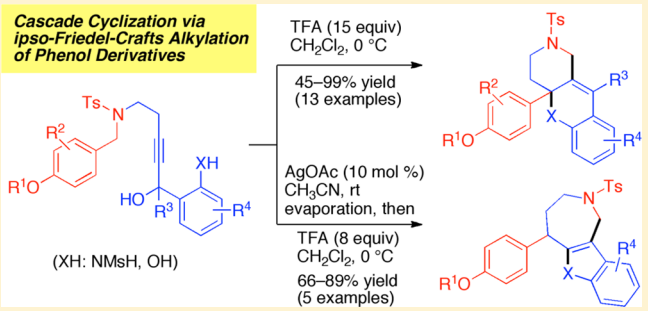
Construction of Divergent Fused Heterocycles via an Acid-Promoted Intramolecular *ipso*-Friedel–Crafts Alkylation of Phenol Derivatives

Takuya Yokosaka, Naoki Shiga, Tetsuhiro Nemoto, and Yasumasa Hamada*

Graduate School of Pharmaceutical Sciences, Chiba University, 1-8-1, Inohana, Chuo-ku, Chiba 260-8675, Japan

Supporting Information

ABSTRACT: Two different cascade cyclization processes were developed using aryl group-substituted propargyl alcohol derivatives with a *p*-hydroxybenzylamine unit as common substrates. Using TFA as an acid promoter, an intramolecular *ipso*-Friedel–Crafts alkylation of phenol derivatives, formation of an iminium cation via a rearomatization-promoted C–C bond cleavage, an aza-Prins reaction, and a 6-membered ring formation proceeded sequentially, producing a variety of fused-tricyclic dihydroquinoline derivatives in 45–99% yield. In addition, a one-pot sequential silver acetate-catalyzed hydroamination/etherification–acid-promoted skeletal rearrangement was examined using the same series of substrates, affording fused-tricyclic indole/benzofuran derivatives in 66–89% yield.



INTRODUCTION

Nitrogen-containing fused heterocycles have high potential for diverse bioactivities and are attractive compounds in medicinal chemistry. The development of an efficient synthetic method for such heterocyclic compounds is therefore an important task in the field of organic synthesis, and extensive efforts have focused on this aim. The cascade reaction is one of the most straightforward approaches to the rapid construction of complex molecules.[1] Several cascade reactions producing nitrogen-containing fused-heterocyclic compounds from simple starting materials have been reported to date.[2]

Spirocyclohexadienone derivatives are useful intermediates in complex molecule synthesis.[3] These spirocyclic compounds are generally synthesized from phenol derivatives through a single-step dearomatization reaction.[4] In addition, the versatile properties of the spirocyclohexadienone unit make this class of compounds suitable intermediates for designing a novel cascade process. As part of our ongoing studies aimed toward the development of efficient and divergent synthetic methods for highly functionalized heterocycles, we recently reported several acid-promoted cascade cyclization reactions.[5] The developed methods were based on a sequential process involving the dearomatization of phenols through an intramolecular *ipso*-Friedel–Crafts alkylation and subsequent formation of an iminium cation via the rearomatization-promoted C–C bond cleavage (Scheme 1). When 3-alkylideneindolenium cations derived from the corresponding 3-indolymethyl alcohol derivatives were used as electrophiles in the intramolecular *ipso*-Friedel–Crafts alkylation step, a Pictet–Spengler reaction proceeded in the final step to give fused-tricyclic indole derivatives [Scheme 1(a)].[5a] On the other hand, when allyl cations were used as electrophiles, the generated iminium cations were entrapped through an intramolecular aza-Prins reaction, affording functionalized pyrrolidine derivatives in a highly diastereoselective manner [Scheme 1(b)].[5b]

Propargyl alcohol derivatives are useful precursors for synthesizing allenyl compounds through an S_N2' process.[6] When aryl group-substituted propargyl alcohol derivatives are utilized as electrophile sources in the acid-promoted intramolecular *ipso*-Friedel–Crafts alkylation of phenols, aromatic ring-conjugated allenyl spirocyclohexadienone derivatives are obtained as initial intermediates. We envisioned that the use of substrates bearing a nucleophilic substituent at the *ortho*-position of the aromatic ring would lead to the formation of allenyl intermediates with an iminium cation unit, which would be converted into fused-heterocyclic compounds via sequential bond-forming events (Scheme 2). Here we report an acid-promoted cascade cyclization to produce fused-tricyclic dihydroquinoline derivatives via intramolecular *ipso*-Friedel–Crafts alkylation of phenol derivatives. In addition, one-pot sequential silver-catalyzed hydroamination/etherification–acid-promoted cascade cyclization using the same substrates was examined, affording fused-tricyclic indole/benzofuran derivatives.

RESULTS AND DISCUSSION

We began our examination with the synthesis of a model substrate **5a** (Scheme 3). After condensation of tosylamide derivative **1** with *p*-methoxybenzyl chloride **2a** (99% yield), a lithium acetylide derived from **3a** was reacted with benzaldehyde derivative **4a** at −78 °C to give propargyl

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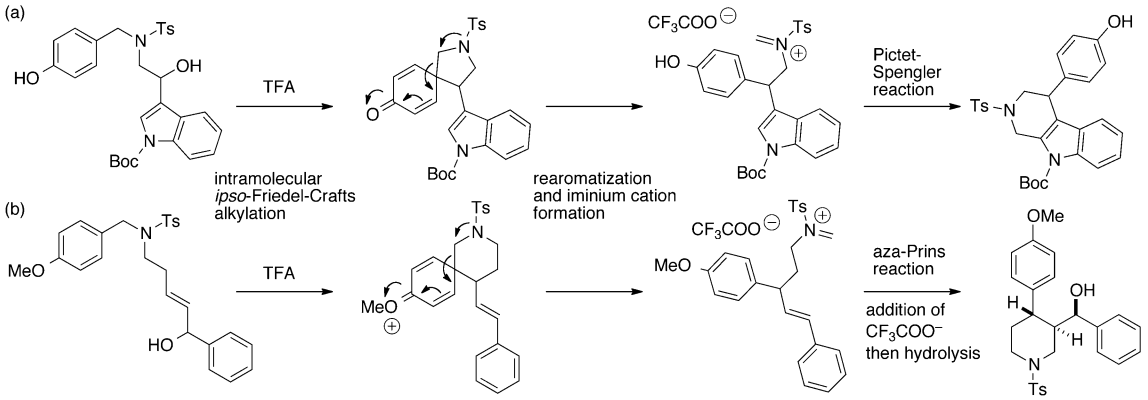
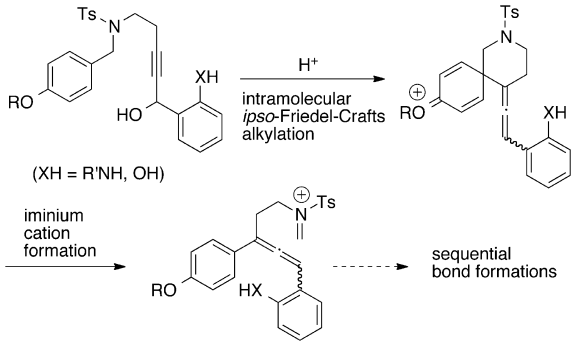
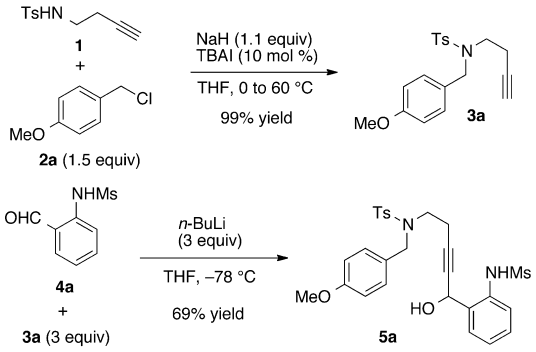
Scheme 1. Background of This Work



Scheme 2. Cascade Reaction Design



Scheme 3. Synthesis of Model Substrate 5a

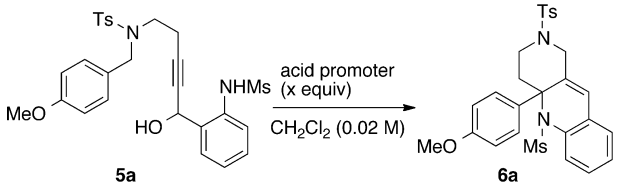


alcohol derivative **5a** in 69% yield. An acid-promoted cascade cyclization was then examined using **5a** as a substrate (Table 1). Compound **5a** was first treated with TFA in CH_2Cl_2 (0.02 M) at 0 °C. Compound **5a** gradually transformed into a single compound in proportion to the increase in the amount of TFA, and the structure of the obtained product was determined to be fused-tricyclic dihydroquinoline derivative **6a**. Using 15 equiv of TFA, **6a** was obtained in 80% yield (entry 3). The use of 1 equiv of $TsOH·H_2O$ resulted in a messy reaction (entry 5). The same cascade cyclization was also examined using Lewis acid catalysts (entries 6−9). Although the reaction proceeded using 20 mol % of $Sc(OTf)_3$, **6a** was obtained in 21% yield after 24 h (entry 6). We thus determined that the reaction conditions in entry 3 were optimum for this cascade cyclization.

With the optimum conditions in hand, we next examined the substrate scope of the cascade cyclization process. Propargyl alcohol derivatives **5b−d** were prepared as shown in Scheme 4. Tosyl amide derivative **1** was reacted with *p-tert*-butyldimethylsilyloxy benzyl acetate **7** under basic conditions to give compound **3b** in 90% yield. A coupling reaction between **3b** and **4a**, followed by deprotection of the TBS group, afforded compound **5b** in 72% yield (2 steps). Compounds **5c** and **5d** were also prepared from the corresponding benzyl chloride derivatives **2b** and **2c** using the same procedure as that for compound **5a**. Tertiary alcohol derivatives **5e−g** were prepared from compound **5a** (Scheme 5). After oxidation of the secondary alcohol with MnO_2, the obtained ketone derivative was treated with 3 equiv of Grignard reagent to give **5e−g** in moderate to high yield. On the other hand, compounds **5h−k** were synthesized from **3a** and benzaldehyde derivatives **4b−e**, and the target propargyl alcohol derivatives were obtained in 84−91% yield. Moreover, compound **3a** was reacted with salicylaldehyde **8a** or acetophenone derivative **8b** under the above-described conditions, providing phenol-type substrate **5l** and **5m** in moderate yield (Scheme 6).

Results using various substrates **5a−m** are summarized in Table 2. In addition to the model substrate **5a**, phenol derivative **5b**, *O*-benzyl derivative **5c**, and *ortho*-substituted anisole derivative **5d** were applicable to this cascade cyclization, and the fused-tricyclic dihydroquinoline derivatives **6a−d** were obtained in 71−80% yield (entries 1−4). The reaction using tertiary alcohol derivatives **5e−g** proceeded under the same conditions, affording the products with a tetrasubstituted olefin **6e−g** in 70−99% yield (entries 5−7). Substrates **5h−k**, bearing

Table 1. Optimization of the Reaction Conditions



entry	acid (*x* equiv)	temp (°C)	time (h)	yield (%)[a]
1	TFA (1)	0	24	trace
2	TFA (5)	0	5	50
3	TFA (15)	0	2	80
4	TFA (25)	0	2	80
5	$TsOH·H_2O$ (1)	0	2	messy
6	$Sc(OTf)_3$ (0.2)	rt	24	21
7	$In(OTf)_3$ (0.2)	rt	24	trace
8	$Yb(OTf)_3$ (0.2)	rt	24	trace
9	$B(C_6F_5)_3$ (0.2)	rt	24	messy

[a]Isolated yield.

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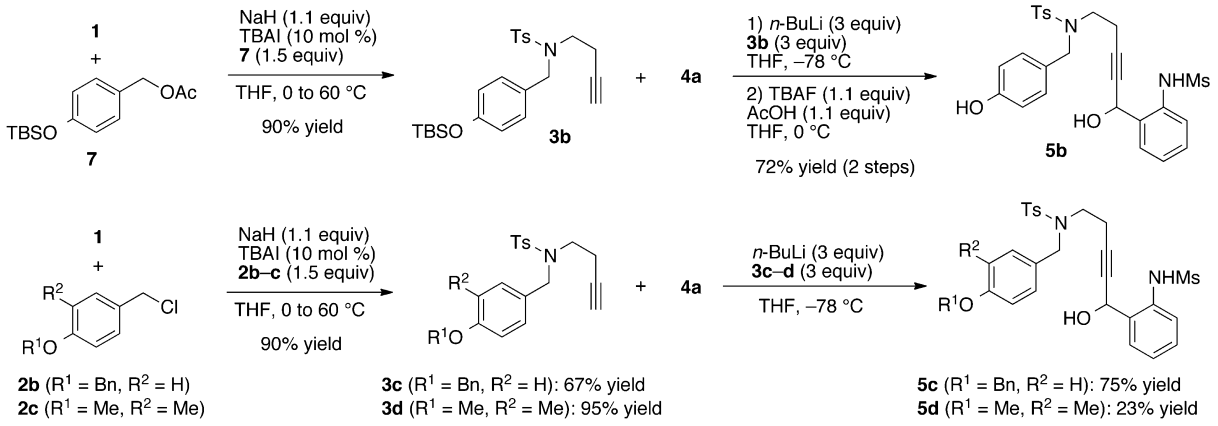
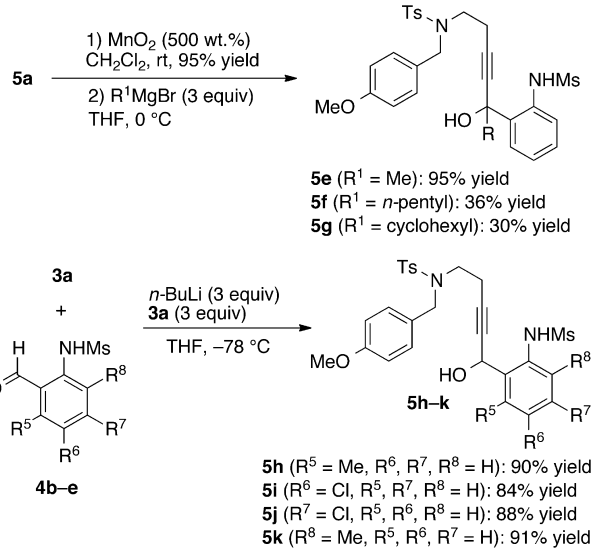
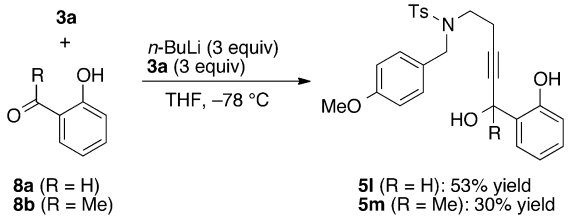
Scheme 4. Synthesis of 5b–d



Scheme 5. Synthesis of 5e–k



Scheme 6. Synthesis of 5l and 5m



electron-donating or electron-withdrawing groups on the aromatic ring of the propargyl alcohol moiety, were also tolerant to this cascade process, providing **6h–k** in 61–77% yield (entries 8–11). Furthermore, compounds **5l** and **5m** were effective substrates for this cascade cyclization, and the corresponding fused-tricyclic 2*H*-chromene derivatives **6l** and **6m** were obtained in 45 and 69% yield, respectively.

A plausible reaction pathway of this cascade cyclization process is shown in Scheme 7. First, acid-promoted intramolecular *ipso*-Friedel–Crafts-type addition of the phenol unit in **5a** to a propargyl cation proceeds through an S_N2' mechanism, affording an allenyl spirocyclohexadienone intermediate **I**. Rearomatization-promoted C–C bond cleavage occurs next to give an iminium cation intermediate **II**. Subsequent aza-Prins reaction of **II** results in the formation of allyl cation intermediates **III** or **IV**. Finally, the tetrasubstituted carbon center is formed through a 6-membered ring formation, producing fused-heterocyclic compound **6a**.[7]

Table 2. Scope and Limitations[a]

Entry	Substrate	Product: Yield
1	**5a**	**6a** (R^1 = Me, R^2, R^3 = H): 80% yield
2[b]	**5b**	**6b** (R^1, R^2, R^3 = H): 74% yield
3	**5c**	**6c** (R^1 = Bn, R^2, R^3 = H): 71% yield
4	**5d**	**6d** (R^1 = Me, R^2 = Me, R^3 = H): 73% yield
5	**5e**	**6e** (R^3 = Me): 99% yield
6	**5f**	**6f** (R^3 = *n*-pentyl): 70% yield
7	**5g**	**6g** (R^3 = cyclohexyl): 86% yield
8	**5h**	**6h**: (R^4 = Me, R^5, R^6, R^7 = H): 73% yield
9	**5i**	**6i**: (R^5 = Cl, R^4, R^6, R^7 = H): 77% yield
10	**5j**	**6j**: (R^6 = Cl, R^4, R^5, R^7 = H): 76% yield
11[c]	**5k**	**6k**: (R^7 = Me, R^4, R^5, R^6 = H): 61% yield
12	**5l**	**6l**: (R^8 = H): 45% yield
13	**5m**	**6m**: (R^8 = Me): 69% yield

[a]Reaction conditions: TFA (15 equiv), CH_2Cl_2 (0.02 M), 0 °C, 1 h. [b]25 equiv of TFA was used. [c]Reaction time: 2 h.

Chan and co-workers recently reported a silver acetate-catalyzed hydroamination reaction in which 1-(2-sulfonylamino)aryl group-substituted propargyl alcohol derivatives were efficiently transformed into (*Z*)-2-alkylidene-1-sulfonylindolin-3-ols.[8] Treatment of the hydroamination adducts with an acid promoter can produce 2-alkylidene 2*H*-indolium cations, leading us to design a novel cascade cyclization using **5** as substrates (Scheme 8). A hydroamination reaction of **5** should proceed in the presence of a catalytic amount of AgOAc, providing (*Z*)-2-alkylidene-1-methansulfonylindolin-3-ol intermediate **A**. After completion of the initial

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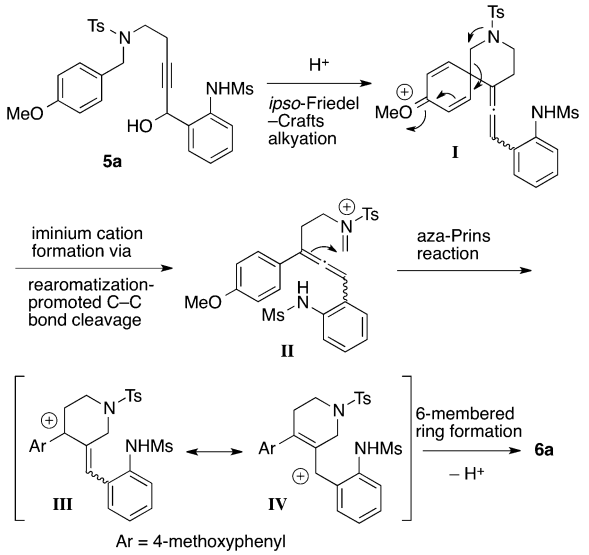
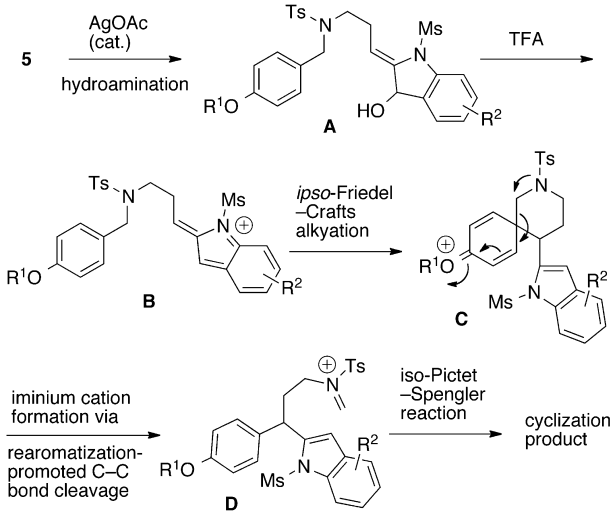
Scheme 7. Plausible Reaction Pathway



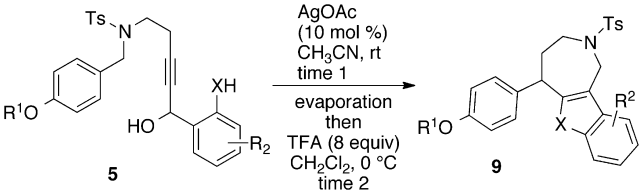
Scheme 8. Cascade Reaction Design



C–N bond formation, the addition of TFA and CH_2Cl_2 to the crude mixture would produce 2-alkylidene indolium cation intermediate **B**. Intramolecular *ipso*-Friedel–Crafts alkylation of phenol would occur subsequently to give spirocyclohexadienone intermediate **C**, which would then be transformed into the corresponding tricyclic adduct through an iminium cation formation–iso-Pictet–Spengler reaction sequence.[9]

We first examined the designed cascade reaction using **5b** as a substrate (Table 3). Hydroamination of **5b** proceeded in the presence of 10 mol % of AgOAc in CH_3CN, providing the corresponding (*Z*)-2-alkylidene-1-methansulfonylindolin-3-ol intermediate. After concentrating the reaction mixture under reduced pressure, the crude mixture was treated with 8 equiv of TFA in CH_2Cl_2 at 0 °C. Fused-tricyclic indole derivative **9b** was obtained in 89% yield (entry 1). Substrates **5c**, **5h**, and **5j** were also applicable to this one-pot cascade process, and the corresponding products **9c**, **9h**, and **9j** were obtained in 74–80% yield. Furthermore, using **5l** as a substrate, silver-catalyzed hydroetherification and subsequent acid-promoted skeletal rearrangement proceeded in a single-pot reaction to give 7-membered ring-fused benzofuran derivative **9l** in 66% yield.

Table 3. One-Pot Cascade Reaction



entry	substrate	time 1[a]	time 2[a]	product: yield[b] (%)
1	**5b**	2 h	24 h	**9b**: 89
2	**5c**	20 min	3.5 h	**9c**: 76
3	**5h**	20 min	8 h	**9h**: 80
4	**5j**	1 h	17 h	**9j**: 74
5	**5l**	2 h	20 h	**9l**: 66

[a]Reaction times were not optimized. [b]Isolated yield.

CONCLUSION

We successfully developed two different cascade cyclization processes using the same propargyl alcohol derivatives as substrates. An intramolecular *ipso*-Friedel–Crafts alkylation of phenol derivatives, formation of an iminium cation via a rearomatization-promoted C–C bond cleavage, an aza-Prins reaction, and a 6-membered ring formation proceeded sequentially in the presence of TFA, producing a variety of fused-tricyclic dihydroquinoline derivatives in 45–99% yield. In addition, a one-pot sequential silver acetate-catalyzed hydroamination/etherification–acid-promoted skeletal rearrangement was examined using the same series of substrates, affording fused-tricyclic indole/benzofuran derivatives in 66–89% yield.

EXPERIMENTAL SECTION

General Methods. Infrared (IR) spectra were recorded on a Fourier transform infrared spectrophotometer, equipped with ATR. NMR spectra were recorded with a 400 MHz spectrometer. Chemical shifts in $CDCl_3$ were reported downfield from TMS (= 0 ppm) for ^1H NMR. For ^{13}C NMR, chemical shifts were reported in the scale relative to the solvent signal [$CHCl_3$ (77.0 ppm)] as an internal reference. Positive-ion mass spectra were recorded by electrospray ionization (ESI-TOF). Column chromatography was performed with 63–230 mesh spherical neutral silica gel. Reactions were carried out in dry solvent. Other reagents were purified by the usual methods.

General Procedure for the Preparation of 3. To a stirred solution of **1**[10] (893 mg, 4.0 mmol) in THF (25 mL) at 0 °C was added NaH (60% in oil, 176 mg, 4.4 mmol). After being stirred for 30 min at 0 °C, **2a** (830 mg, 5.3 mmol) in THF (5 mL) and TBAI (148 mg, 0.4 mmol) were added to the reaction mixture at the same temperature. After being stirred for required time at 60 °C, the reaction mixture was quenched with H_2O at room temperature, and extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (SiO_2, *n*-hexane/EtOAc = 8/1) to give *N*-(but-3-yn-1-yl)-*N*-(4-methoxybenzyl)-4-methylbenzenesulfonamide **3a** (1.37 g, 99% yield) as white solid: mp 81–83 °C; R_f = 0.64 (*n*-hexane/EtOAc = 1/1); ^1H NMR (400 MHz, $CDCl_3$) δ 1.89 (t, J = 2.4 Hz, 1H), 2.22 (td, J = 7.6, 2.4 Hz, 2H), 2.44 (s, 3H), 3.24 (t, J = 7.6 Hz, 2H), 3.79 (s, 3H), 4.29 (s, 2H), 6.84 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 7.73 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.0, 21.5, 46.4, 51.9, 55.2, 70.0, 80.9, 114.0 (2C), 127.1 (2C), 127.8, 129.6 (2C), 129.7 (2C), 136.7, 143.4, 159.3; IR (ATR) ν 3821, 2926, 1611, 1511, 1335, 1246, 1154, 1092, 1032, 914, 813, 737 cm^{-1}; HRMS (ESI-TOF) m/z [M + Na]$^+$ Calcd for $C_{19}H_{21}NNaO_3S^+$ 366.1134, found 366.1118.

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*N-(But-3-yn-1-yl)-N-(4-((tert-butyldimethylsilyl)oxy)benzyl)-4-methylbenzenesulfonamide (**3b**).* This compound was synthesized from **1** (670 mg, 3.0 mmol) and **7**[5b] (1.26 g, 4.5 mmol) according to the general procedure and was obtained in 90% yield (1.20 g). Colorless oil: R_f = 0.50 (*n*-hexane/EtOAc = 2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.19 (s, 6H), 0.98 (s, 9H), 1.88 (t, J = 2.4 Hz, 1H), 2.21 (td, J = 7.6, 2.4 Hz, 2H), 2.44 (s, 3H), 3.24 (t, J = 7.6 Hz, 2H), 4.28 (s, 2H), 6.78 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 7.73 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.5 (2C), 18.2, 19.1, 21.5, 25.6 (3C), 46.5, 52.0, 70.0, 80.9, 120.3 (2C), 127.2 (2C), 128.6, 129.7 (2C), 129.8 (2C), 136.9, 143.4, 155.5; IR (ATR) ν 3290, 2929, 1607, 1508, 1338, 1254, 1156, 1092, 908, 837, 779, 743 cm^{-1}; HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_{24}H_{33}NNaO_3SSi^+$ 466.1843, found 466.1827.

*N-(But-3-yn-1-yl)-N-(4-benzyloxybenzyl)-4-methylbenzenesulfonamide (**3c**).* This compound was synthesized from **1** (670 mg, 3.0 mmol) and **2b** (1.02 g, 4.4 mmol) according to the general procedure and was obtained in 67% yield (850 mg). White solid: mp 116−117 °C; R_f = 0.51 (*n*-hexane/EtOAc = 2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.88 (t, J = 2.0 Hz, 1H), 2.22 (td, J = 7.6, 2.0 Hz, 2H), 2.42 (s, 3H), 3.24 (t, J = 7.6 Hz, 2H), 4.28 (s, 2H), 5.04 (s, 2H), 6.91 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 7.28−7.33 (m, 1H), 7.31 (d, J = 8.0 Hz, 2H), 7.35−7.43 (m, 4H), 7.72 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.0, 21.5, 46.4, 51.9, 69.9, 70.0, 80.9, 114.9 (2C), 127.1 (2C), 127.4 (2C), 127.9, 128.1, 128.5 (2C), 129.7 (2C), 129.7 (2C), 136.7, 136.7, 143.4, 158.5; IR (ATR) ν 3290, 1610, 1509, 1336, 1240, 1155, 1093, 915, 814, 741, 697 cm^{-1}; HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_{25}H_{25}NNaO_3S^+$ 442.1447, found 442.1457.

*N-(But-3-yn-1-yl)-N-(4-methoxy-3-methylbenzyl)-4-methylbenzenesulfonamide (**3d**).* This compound was synthesized from **1** (670 mg, 3.0 mmol) and **2c** (768 mg, 4.5 mmol) according to the general procedure and was obtained in 95% yield (1.02 g). White solid: mp 91−94 °C; R_f = 0.51 (*n*-hexane/EtOAc = 2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.90 (t, J = 2.0 Hz, 1H), 2.16 (s, 3H), 2.23 (td, J = 8.4, 2.0 Hz, 2H), 2.44 (s, 3H), 3.24 (t, J = 8.4 Hz, 2H), 3.81 (s, 3H), 4.26, (s, 2H), 6.74 (d, J = 8.0 Hz, 1H), 6.97 (d, J = 2.0 Hz, 1H), 7.04 (dd, J = 8.0, 2.0 Hz, 1H), 7.32 (d, J = 8.0 Hz, 2H), 7.74 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.1, 19.0, 21.5, 46.3, 51.9, 55.3, 70.0, 81.0, 109.7, 126.9, 126.9, 127.1 (2C), 127.2, 129,7 (2C), 130.7, 136.9, 143, 3, 157.5; IR (ATR) ν 3281, 2926, 1505, 1336, 1253, 1156, 1094, 1033, 922, 814, 736, 657; HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_{20}H_{23}NNaO_3S^+$ 380.1291, found 380.1280.

Preparation of Compound 4. Compound **4a** is a known compound.[11] Compounds **4b−e** were synthesized from the known *ortho*-aminobenzoic acid methyl ester derivatives, prepared from the corresponding *ortho*-aminobenzoic acid derivatives, according to the following procedures.

General Procedure. To a stirred solution of 2-amino-4-chlorobenzoic acid (2.00 g, 11.7 mmol) in MeOH (30 mL) at 0 °C was added thionyl chloride (5 mL, 70.2 mmol), and the resulting mixture was refluxed for 7 h. After concentration of the reaction mixture in vacuo, the obtained residue was used for the next reaction without purification. To a stirred solution of the obtained product in pyridine (5 mL) and $CHCl_3$ (5 mL) at 0 °C was added methanesulfonyl chloride (1.0 mL, 12.9 mmol), and the resulting mixture was stirred for 12 h at room temperature. The reaction was quenched by the addition of 1 N aq. $KHSO_4$ and the resulting mixture was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, *n*-hexane/EtOAc = 10/1 to 6/1) to give the sulfonamide derivative (1.72g, 55% yield). To a stirred solution of $LiBH_4$ (283 mg, 13.0 mmol) in THF (10 mL) at 0 °C was added a THF solution of the sulfonamide derivative (1.72 g, 6.49 mmol in 20 mL of THF), and the resulting solution was refluxed for 12 h. The reaction was quenched by the addition of MeOH and 1 N aq. $KHSO_4$, and the resulting mixture was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and then concentrated under reduced pressure. The residue was roughly purified by short pad of silica (SiO_2, *n*-hexane/EtOAc = 2/1), and the obtained residue was washed with CH_2Cl_2 to give pure alcohol derivative as white solid (0.461 g, 30% yield). To a stirred solution of the obtained product (461 mg, 1.96 mmol) in CH_2Cl_2 (14 mL) and THF (7 mL) at room temperature was added MnO_2 (2.3 g). After 12 h, the reaction mixture was filtered through a pad of Celite and concentrated in vacuo. The residue was purified by silica gel column chromatography (SiO_2, *n*-hexane/EtOAc = 4/1) to give *N*-(5-chloro-2-formylphenyl)methanesulfonamide **4d** (386 mg, 84% yield) as pale green solid: mp 95−96 °C; R_f = 0.47 (*n*-hexane/EtOAc = 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.16 (s, 3H), 7.23 (dd, J = 8.0, 1.2 Hz, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 1.2 Hz, 1H), 9.88 (s, 1H), 10.73 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.59, 116.8, 119.7, 123.2, 137.4, 141.1, 143.0, 193.9; IR (ATR) ν 3161, 1669, 1598, 1567, 1492, 1390, 1335, 1150, 1088, 943, 822 cm^{-1}; HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_8H_8ClNNaO_3S^+$ 255.9806, found 255.9831.

*N-(2-Formyl-3-methylphenyl)methanesulfonamide (**4b**).* This compound was synthesized from the commercially available 2-amino-6-methylbenzoic acid (1.00 g, 6.62 mmol) according to the general procedure and was obtained in 39% yield (4 steps, 556 mg). White solid: mp 107−109 °C; R_f = 0.34 (*n*-hexane/EtOAc = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.69 (s, 3H), 3.09 (s, 3H), 6.97 (d, J = 8.0 Hz, 1H), 7.48 (dd, J = 8.0, 8.0 Hz, 1H), 7.58 (d, J = 8.0 Hz, 1H), 10.43 (s, 1H), 11.20 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.0, 40.2, 115.3, 119.0, 125.7, 136.4, 141.0, 144.1, 194.0; IR (ATR) ν 3109, 1638, 1599, 1467, 1373, 1198, 1146, 1040, 983, 860, 791 cm^{-1}; HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_9H_{11}NNaO_3S^+$ 236.0352, found 236.0363.

*N-(4-Chloro-2-formylphenyl)methanesulfonamide (**4c**).* This compound was synthesized from the commercially available 2-amino-5-chlorobenzoic acid (1.00 g, 5.83 mmol) according to the general procedure and was obtained in 10% yield (4 steps, 133 mg). Pale green solid: mp 108−110 °C; R_f = 0.47 (*n*-hexane/EtOAc = 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.12 (s, 3H), 7.58 (dd, J = 9.2, 2.8 Hz, 1H), 7.70 (d, J = 2.8 Hz, 1H), 7.73 (d, J = 9.2 Hz, 1H), 9.88 (s, 1H), 10.48 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.5, 118.6, 122.5, 128.4, 135.5, 136.0, 138.6, 193.8; IR (ATR) ν 3143, 1672, 1573, 1482, 1381, 1330, 1186, 1150, 965, 866 cm^{-1}; HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_8H_8ClNNaO_3S$ 255.9806$^+$, found 255.9810.

*N-(2-Formyl-6-methylphenyl)methanesulfonamide (**4e**).* This compound was synthesized from the commercially available 2-amino-3-methylbenzoic acid (1.00 g, 6.62 mmol) according to the general procedure and was obtained in 39% yield (4 steps, 556 mg). White solid: mp 145−147 °C; R_f = 0.26 (*n*-hexane/EtOAc = 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.54 (s, 3H), 2.91 (s, 3H), 7.43 (dd, J = 7.6, 7.6 Hz, 1H), 7.59 (d, J = 7.6 Hz, 1H), 7.65 (d, J = 7.6 Hz, 1H), 8.44 (s, 1H), 10.04 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 39.7, 127.2, 129.5, 133.4, 135.8, 138.3, 138.7, 194.4; IR (ATR) ν 3264, 1684, 1382, 1321, 1243, 1152, 975, 894, 768 cm^{-1}; HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_9H_{11}NNaO_3S^+$ 236.0352, found 236.0360.

Preparation of 5a, 5c, 5d, and 5h−m. General Procedure. To a stirred solution of alkyne **3a** (1.03 g, 3.0 mmol) in THF (5 mL) at −78 °C was added *n*-BuLi (1.86 mL, 1.6 M in THF, 3.0 mmol). After being stirred for 30 min at −78 °C, to the reaction mixture was added **4a** (200 mg, 1.0 mmol) in THF (5 mL) at the same temperature. After being stirred for 30 min, the reaction mixture was quenched with saturated aqueous NH_4Cl, and extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (SiO_2, *n*-hexane/EtOAc = 4/1) to give *N*-(5-hydroxy-5-(2-(methylsulfonamido)phenyl)pent-3-yn-1-yl)-*N*-(4-methoxybenzyl)-4-methylbenzenesulfonamide **5a** (444 mg, 82% yield) as white amorphous: R_f = 0.27 (*n*-hexane/EtOAc = 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28 (t, J = 6.8 Hz, 2H), 2.45 (s, 3H), 3.00 (s, 3H), 3.12 (br-s, 1H), 3.29 (t, J = 6.8 Hz, 2H), 3.78 (s, 3H), 4.22 (d, J = 14.4 Hz, 1H), 4.26 (d, J = 14.4 Hz, 1H), 5.51 (s, 1H), 6.81 (d, J = 8.8 Hz, 2H), 7.13 (d, J = 8.8 Hz, 2H), 7.14 (t, J = 8.0 Hz, 1H), 7.33 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.0 Hz, 1H), 7.39 (t, J = 8.0 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.73 (d, J = 8.4 Hz, 2H), 7.86 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.5, 21.5, 39.9, 46.4, 51.9, 55.3, 63.8, 80.3, 86.0, 114.1 (2C), 121.6, 124.9, 127.2 (2C), 129.6, 128.8, 129.7 (2C), 129.8,

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129.9 (2C), 130.0, 135.9, 136.4, 143.6, 159.4; IR (ATR) ν 3455, 3281, 1610, 1512, 1328, 1248, 1152, 1093, 973, 816, 742, 657 cm^{-1}; HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_{27}H_{30}N_2NaO_6S_2^+$ 565.1437, found 565.1440.

*N-(5-Hydroxy-5-(2-(methylsulfonamido)phenyl)pent-3-yn-1-yl)-N-(4-benzyloxybenzyl)-4-methylbenzenesulfonamide (**5c**).* This compound was synthesized from **3c** (523 mg, 1.2 mmol) and **4a** (80 mg, 0.4 mmol) according to the general procedure and was obtained in 75% yield (186 mg). White amorphous: R_f = 0.44 (*n*-hexane/EtOAc = 1/1); ^1H NMR (400 MHz, $CDCl_3$) δ 2.28 (t, J = 7.2 Hz, 2H), 2.43 (s, 3H), 2.98 (s, 3H), 3.26 (br-s, 1H), 3.28 (t, J = 7.2 Hz, 2H), 4.21 (d, J = 14.8 Hz, 1H), 4.26 (d, J = 14.8 Hz, 1H), 5.02 (s, 2H), 5.50 (s, 1H), 6.89 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 8.4 Hz, 2H), 7.14 (t, J = 7.6 Hz, 1H), 7.31−7.42 (m, 9H), 7.59 (d, J = 7.6 Hz, 1H), 7.72 (d, J = 8.4 Hz, 2H), 7.87 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.5, 21.5, 39.8, 46.4, 51.9, 63.7, 70.0, 80.3, 85.9, 115.0 (2C), 121.6, 124.9, 127.2 (2C), 127.5 (2C), 127.9, 128.0, 128.6 (2C), 128.8, 129.7 (2C), 129.8, 129.8 (2C), 130.1, 135.8, 136.4, 136.7, 143.6, 158.5; IR (ATR) ν 3426, 3273, 1609, 1509, 1326, 1151, 1092, 971, 916, 815, 738, 697 cm^{-1}; HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_{33}H_{34}N_2NaO_6S_2^+$ 641.1750, found 641.1746.

*N-(5-Hydroxy-5-(2-(methylsulfonamido)phenyl)pent-3-yn-1-yl)-N-(4-methoxy-3-methylbenzyl)-4-methylbenzenesulfonamide (**5d**).* This compound was synthesized from **3d** (357 mg, 1.5 mmol) and **4a** (100 mg, 0.5 mmol) according to the general procedure and was obtained in 23% yield (64 mg). White amorphous: R_f = 0.43 (*n*-hexane/EtOAc = 1/1); ^1H NMR (400 MHz, $CDCl_3$) δ 2.13 (s, 3H), 2.31 (t, J = 7.2 Hz, 2H), 2.45 (s, 3H), 3.01 (s, 3H), 3.07 (s, 1H), 3.30 (t, J = 7.2 Hz, 2H), 3.80 (s, 3H), 4.20 (d, J = 14.4 Hz, 1H), 4.25 (d, J = 14.4 Hz, 1H), 5.52 (s, 1H), 6.72 (d, J = 8.0 Hz, 1H), 6.86 (s, 1H), 6.99 (d, J = 8.0 Hz, 1H), 7.15 (t, J = 8.0 Hz, 1H), 7.33 (d, J = 8.0 Hz, 2H), 7.34 (t, J = 8.0 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.61 (d, J = 8.0 Hz, 1H), 7.74 (d, J = 8.0 Hz, 2H), 7.86 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.5, 19.8, 21.8, 40.2, 46.5, 52.1, 55.6, 64.1, 80.6, 86.5, 110.1, 121.9, 125.2, 127.3, 127.3, 127.5 (2C), 129.1, 130.1 (2C), 130.1, 130.1, 130.2, 131.0, 136.2, 136.9, 143.9, 157.8; IR (ATR) ν 3438, 3281, 1503, 1325, 1253, 1150, 1092, 971, 920, 814, 732, 656 cm^{-1}; HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_{28}H_{32}N_2NaO_6S_2^+$ 579.1594, found 579.1620.

*N-(5-Hydroxy-5-(2-methyl-6-(methylsulfonamido)phenyl)pent-3-yn-1-yl)-N-(4-methoxybenzyl)-4-methylbenzenesulfonamide (**5h**).* This compound was synthesized from **3a** (515 mg, 1.5 mmol) and **4b** (107 mg, 0.5 mmol) according to the general procedure and was obtained in 90% yield (249 mg). White amorphous: R_f = 0.36 (*n*-hexane/EtOAc = 1/1); ^1H NMR (400 MHz, $CDCl_3$) δ 2.20 (t, J = 7.2 Hz, 2H), 2.35 (s, 3H), 2.44 (s, 3H), 2.93 (s, 3H), 3.24 (t, J = 7.2 Hz, 2H), 3.37 (br-s, 1H), 3.78 (s, 3H), 4.17 (d, J = 14.8 Hz, 1H), 4.24 (d, J = 14.8 Hz, 1H), 5.85 (s, 1H), 6.80 (d, J = 8.4 Hz, 2H), 6.95 (d, J = 8.0 Hz, 1H), 7.10 (d, J = 8.4 Hz, 2H), 7.18 (t, J = 8.0 Hz, 1H), 7.32 (d, J = 8.0 Hz, 2H), 7.48 (d, J = 8.0 Hz, 1H), 7.71 (d, J = 8.0 Hz, 2H), 8.37 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.6, 20.0, 21.5, 39.4, 46.3, 51.9, 55.2, 60.0, 80.7, 84.4, 114.0 (2C), 119.6, 127.1 (2C), 127.2, 127.6, 128.1, 129.0, 129.7 (2C), 129.8 (2C), 136.3, 136.3, 136.4, 143.6, 159.3; IR (ATR) ν 3446, 3255, 1586, 1512, 1470, 1322, 1247, 1150, 1092, 979, 815, 735 cm^{-1}; HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_{28}H_{32}N_2NaO_6S_2^+$ 579.1594, found 579.1594.

*N-(5-(5-Chloro-2-(methylsulfonamido)phenyl)-5-hydroxypent-3-yn-1-yl)-N-(4-methoxybenzyl)-4-methylbenzenesulfonamide (**5i**).* This compound was synthesized from **3a** (566 mg, 1.65 mmol) and **4c** (128 mg, 0.55 mmol) according to the general procedure and was obtained in 84% yield (268 mg). White amorphous: R_f = 0.08 (*n*-hexane/EtOAc = 2/1); ^1H NMR (400 MHz, $CDCl_3$) δ 2.27 (t, J = 6.8 Hz, 2H), 2.44 (s, 3H), 3.00 (s, 3H), 3.28 (t, J = 6.8 Hz, 2H), 3.46 (br-s, 1H), 3.78 (s, 3H), 4.21 (d, J = 14.4 Hz, 1H), 4.25 (d, J = 14.4 Hz, 1H), 5.47 (s, 1H), 6.81 (d, J = 8.0 Hz, 2H), 7.12 (d, J = 8.0 Hz, 2H), 7.29 (dd, J = 8.8, 2.0 Hz, 1H), 7.33 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 2.0 Hz, 1H), 7.53 (d, J = 8.8 Hz, 1H), 7.72 (d, J = 8.0 Hz, 2H), 7.85 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.5, 21.5, 40.0, 46.3, 51.9, 55.3, 63.0, 79.7, 86.5, 114.1 (2C), 123.2, 127.2 (2C), 127.5, 128.6, 129.5, 129.7 (2C), 129.9 (2C), 130.3, 131.9, 134.4, 136.2, 143.7, 159.4; IR (ATR) ν 3455, 3281, 1512, 1488, 1328, 1248, 1153, 1092, 972, 816, 735 cm^{-1}; HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_{27}H_{29}ClN_2NaO_6S_2^+$ 599.1048, found 599.1038.

*N-(5-(4-Chloro-2-(methylsulfonamido)phenyl)-5-hydroxypent-3-yn-1-yl)-N-(4-methoxybenzyl)-4-methylbenzenesulfonamide (**5j**).* This compound was synthesized from **3a** (515 mg, 1.5 mmol) and **4d** (117 mg, 0.5 mmol) according to the general procedure and was obtained in 88% yield (255 mg). White amorphous: R_f = 0.39 (*n*-hexane/EtOAc = 1/1); ^1H NMR (400 MHz, $CDCl_3$) δ 2.27 (t, J = 7.2 Hz, 2H), 2.45 (s, 3H), 3.02 (s, 3H), 3.28 (t, J = 7.2 Hz, 2H), 3.43 (d, J = 4.0 Hz, 1H), 3.78 (s, 3H), 4.20 (d, J = 14.8 Hz, 1H), 4.25 (d, J = 14.8 Hz, 1H), 5.46 (d, J = 4.0 Hz, 1H), 6.81 (d, J = 8.4 Hz, 2H), 7.09 (dd, J = 8.0, 2.0 Hz, 1H), 7.11 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.0 Hz, 1H), 7.33 (d, J = 8.4 Hz, 2H), 7.62 (d, J = 2.0 Hz, 1H), 7.72 (d, J = 8.4 Hz, 2H), 8.02 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.5, 21.5, 40.1, 46.3, 51.9, 55.3, 63.3, 79.9, 86.3, 114.0 (2C), 121.0, 124.6, 127.2 (2C), 127.5, 127.9, 129.7 (2C), 129.8, 129.9 (2C), 135.4, 136.2, 137.1, 143.7, 159.4; IR (ATR) ν 3437, 3281, 1599, 1512, 1493, 1326, 1247, 1151, 1091, 968, 814, 734 cm^{-1}; HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_{27}H_{29}ClN_2NaO_6S_2^+$ 599.1048, found 599.1050.

*N-(5-Hydroxy-5-(3-methyl-2-(methylsulfonamido)phenyl)pent-3-yn-1-yl)-N-(4-methoxybenzyl)-4-methylbenzenesulfonamide (**5k**).* This compound was synthesized from **3a** (515 mg, 1.5 mmol) and **4e** (107 mg, 0.5 mmol) according to the general procedure and was obtained in 91% yield (255 mg). White amorphous: R_f = 0.20 (*n*-hexane/EtOAc = 1/1); ^1H NMR (400 MHz, $CDCl_3$) δ 2.30 (t, J = 7.2 Hz, 2H), 2.43 (s, 3H), 2.44 (s, 3H), 3.14 (s, 3H), 3.25 (br-s, 1H), 3.27 (t, J = 7.2 Hz, 2H), 3.78 (s, 3H), 4.24 (s, 2H), 5.79 (s, 1H), 6.79 (d, J = 8.0 Hz, 2H), 6.87 (s, 1H), 7.13 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 5.2 Hz, 1H), 7.25 (d, J = 5.2 Hz, 1H), 7.32 (d, J = 8.0 Hz, 2H), 7.54 (t, J = 5.2 Hz, 1H), 7.72 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.0, 19.5, 21.5, 41.7, 46.6, 52.0, 55.2, 61.9, 81.0, 84.6, 114.0 (2C), 126.6, 127.1 (2C), 127.8, 128.1, 129.6 (2C), 129.8 (2C), 131.5, 132.1, 136.4, 137.2, 138.9, 143.5, 159.3; IR (ATR) ν 3464, 3255, 1586, 1512, 1470, 1322, 1247, 1150, 1092, 979, 815, 735 cm^{-1}; HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_{28}H_{32}N_2NaO_6S_2^+$ 579.1594, found 579.1567.

*N-(5-Hydroxy-5-(2-hydroxyphenyl)pent-3-yn-1-yl)-N-(4-methoxybenzyl)-4-methylbenzenesulfonamide (**5l**).* This compound was synthesized from **3a** (515 mg, 1.5 mmol) and **8a** (61 mg, 0.5 mmol) according to the general procedure and was obtained in 53% yield (123 mg). White amorphous: R_f = 0.12 (*n*-hexane/EtOAc = 2/1); ^1H NMR (400 MHz, $CDCl_3$) δ 2.30 (t, J = 6.8 Hz, 2H), 2.43 (s, 3H), 3.27 (t, J = 6.8 Hz, 2H), 3.47 (br-s, 1H), 3.77 (s, 3H), 4.25 (s, 2H), 5.57 (s, 1H), 6.80 (d, J = 8.8 Hz, 2H), 6.84−6.88 (m, 2H), 7.12 (d, J = 8.8 Hz, 2H), 7.18−7.24 (m, 2H), 7.30 (d, J = 8.4 Hz, 2H), 7.52 (br-s, 1H), 7.71 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.4, 21.5, 46.3, 51.8, 55.2, 63.9, 80.1, 85.2, 114.0 (2C), 117.0, 120.0, 124.6, 127.1 (2C), 127.5, 127.7, 129.6 (2C), 129.8 (2C), 129.8, 136.6, 143.6, 155.1, 159.3; IR (ATR) ν 3403, 1610, 1512, 1458, 1245, 1152, 1092, 986, 915, 814, 732 cm^{-1}; HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_{26}H_{27}NNaO_5S^+$ 488.1502, found 488.1492.

*N-(5-Hydroxy-5-(2-hydroxyphenyl)hex-3-yn-1-yl)-N-(4-methoxybenzyl)-4-methylbenzenesulfonamide (**5m**).* This compound was synthesized from **3a** (515 mg, 1.5 mmol) and **8b** (68 mg, 0.5 mmol) according to the general procedure and was obtained in 30% yield (71 mg). White amorphous: R_f = 0.28 (*n*-hexane/EtOAc = 2/1); ^1H NMR (400 MHz, $CDCl_3$) δ 1.79 (s, 3H), 2.31 (t, J = 6.8 Hz, 2H), 2.43 (s, 3H), 3.25−3.34 (m, 2H), 3.78 (s, 3H), 3.79 (s, 1H), 4.21 (d, J = 14.8 Hz, 1H), 4.28 (d, J = 14.8 Hz, 1H), 6.81 (d, J = 8.8 Hz, 2H), 6.83−6.87 (m, 2H), 7.13 (d, J = 8.8 Hz, 2H), 7.18 (t, J = 8.0 Hz, 1H), 7.31 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 7.6 Hz, 1H), 7.72 (d, J = 8.4 Hz, 2H), 8.53 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.3, 21.5, 31.4, 46.4, 51.7, 55.2, 72.4, 83.4, 84.3, 114.0 (2C), 117.6, 119.5, 126.8, 127.1 (2C), 127.7, 128.0, 129.4, 129.6 (2C), 129.8 (2C), 136.6, 143.5, 154.8, 159.3; IR (ATR) ν 3325, 1611, 1512, 1333, 1243, 1152, 1092, 1034, 913, 813, 734 cm^{-1}; HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_{27}H_{29}NNaO_5S^+$ 502.1659, found 502.1662.

Preparation of 5b. To a stirred solution of alkyne **3b** (667 mg, 1.5 mmol) in THF (5 mL) at −78 °C was added *n*-BuLi (0.91 mL, 1.6 M

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in THF, 1.5 mmol). After being stirred for 30 min at −78 °C, to the reaction mixture was added aldehyde **4a** (100 mg, 0.5 mmol) in THF (5 mL) at the same temperature. After being stirred for 30 min, the reaction mixture was quenched with saturated aqueous NH_4Cl, and extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was passed through a short pad of silica gel. After concentration in vacuo, the obtained product was utilized for the next reaction without further purification. TBAF (0.55 mL, 1.0 M in THF, 0.55 mmol) was added to a stirred solution of the crude product and AcOH (31 μL, 0.55 mmol) in THF (10 mL) at 0 °C. After being stirred for 30 min at room temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl, and extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (SiO_2, *n*-hexane/EtOAc = 2/1) to give the desired products *N*-(5-hydroxy-5-(2-(methylsulfonamido)phenyl)pent-3-yn-1-yl)-*N*-(4-hydroxybenzyl)-4-methylbenzenesulfonamide **5b** (165 mg, 72% yield) as white amorphous: R_f 0.19 (*n*-hexane/EtOAc = 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23 (t, J = 6.8 Hz, 2H), 2.43 (s, 3H), 2.98 (s, 3H), 3.23 (t, J = 6.8 Hz, 2H), 3.55 (s, 1H), 4.15 (d, J = 15.2 Hz, 1H), 4.19 (d, J = 15.2 Hz, 1H), 5.50 (s, 1H), 6.12 (s, 1H), 6.75 (d, J = 8.4 Hz, 2H), 7.06 (d, J = 8.4 Hz, 2H), 7,14 (t, J = 7.6 Hz, 1H), 7.29−7.33 (m, 3H), 7.37 (d, J = 8.0 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.71 (d, J = 7.6 Hz, 2H), 7.89 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.6, 21.5, 39.8, 46.7, 52.3, 63.5, 80.2, 85.7, 115.6 (2C), 121.9, 125.2, 127.1 (2C), 127.5, 128.8, 129.8, 129.9 (2C), 129.9 (2C), 130.5, 135.5, 136.0, 143.8, 155.7; IR (ATR) ν 3437, 3307, 1597, 1516, 1323, 1149, 1192, 975, 816, 736 cm^{-1}; HRMS (ESI-TOF) m/z [M + Na]$^+$ Calcd for $C_{26}H_{28}N_2NaO_6S_2^+$ 551.1281, found 551.1290.

Preparation of 5e−g. General Procedure. To a stirred solution of **5a** (980 mg, 2.4 mmol) in CH_2Cl_2 (20 mL) at room temperature was added MnO_2 (5.00 g, ca. 500 wt %). After 1 h, the reaction mixture was filtered through a pad of Celite and concentrated in vacuo. The residue was purified by silica gel column chromatography (SiO_2, *n*-hexane/EtOAc = 2.5/1) to give the desired ketone derivative (720 mg, 95% yield) as white amorphous: R_f 0.35 (*n*-hexane/EtOAc = 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 2.57 (t, J = 6.8 Hz, 2H), 3.08 (s, 3H), 3.36 (t, J = 6.8 Hz, 2H), 3.78 (s, 3H), 4.28 (s, 2H), 6.82 (d, J = 8.0 Hz, 2H), 6.83−7.19 (m, 3H), 7.34 (d, J = 8.0 Hz, 2H), 7.57−7.61 (m, 1H), 7.72−8.23, (m, 3H), 8.25 (d, J = 7.2 Hz, 1H), 10.9 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4, 21.5, 40.2, 45.9, 52.6, 55.2, 80.5, 95.0, 114.2 (2C), 117.3, 121.8, 122.6, 127.2 (2C), 127.5, 129.8 (2C), 129.9 (2C), 135.5, 136.1, 136.2, 140.9, 143.8, 159.5. 180.5; IR (ATR) ν 1614, 1490, 1335, 1247, 1152, 1092, 965, 816, 731 cm^{-1}; HRMS (ESI-TOF) m/z [M + Na]$^+$ Calcd for $C_{27}H_{28}N_2NaO_6S_2^+$ 563.1281, found 563.1277. To a stirred solution of the obtained ketone derivative (176 mg, 0.32 mmol) in THF (5.0 mL) at 0 °C was added MeMgBr (1.1 mL, 1.0 M in THF, 1.14 mmol). After being stirred for 30 min, the reaction mixture was quenched with saturated aqueous NH_4Cl, and extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (SiO_2, *n*-hexane/EtOAc = 2.5/1) to give *N*-(5-hydroxy-5-(2-(methylsulfonamido)phenyl)hex-3-yn-1-yl)-*N*-(4-methoxybenzyl)-4-methylbenzenesulfonamide **5e** (173 mg, 95% yield) as white amorphous: R_f = 0.44 (*n*-hexane/EtOAc = 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.86 (s, 3H), 2.29 (t, J = 6.8 Hz, 2H), 2.44 (s, 3H), 3.02 (s, 3H), 3.31 (t, J = 6.8 Hz, 2H), 3.55 (s, 1H), 3.78 (s, 3H), 4.21 (d, J = 14.8 Hz, 1H), 4.28 (d, J = 14.8 Hz, 1H), 6.81 (d, J = 8.8 Hz, 2H), 7.08 (td, J = 8.0, 1.6 Hz, 1H), 7.12 (d, J = 8.8 Hz, 2H), 7.30 (td, J = 8.0, 1.6 Hz, 1H), 7.33 (d, J = 8.4 Hz, 2H), 7.54 (dd, J = 8.0, 1.6 Hz, 1H), 7.62 (dd, J = 8.0, 1.6 Hz, 1H), 7.73 (d, J = 8.4 Hz, 2H), 8.88 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.3, 21.5, 31.5, 39.8, 46.4, 51.7, 55.3, 71.0, 83.7, 84.7, 114.0 (2C), 119.5, 123.6, 127.2 (2C), 127.3, 127.7, 129.2, 129.6 (2C), 129.8 (2C), 131.5, 136.0, 136.6, 143.6, 159.4; IR (ATR) ν 3437, 3239, 1610, 1512, 1330, 1247, 1151, 1092, 1033, 971, 816, 738 cm^{-1}; HRMS (ESI-TOF) m/z [M + Na]$^+$ Calcd for $C_{28}H_{32}N_2NaO_6S_2^+$ 579.1594, found 579.1612.

*N-(5-Hydroxy-5-(2-(methylsulfonamido)phenyl)dec-3-yn-1-yl)-N-(4-methoxybenzyl)-4-methylbenzenesulfonamide (**5f**).* This compound was synthesized from the ketone derivative (157 mg, 0.29 mmol) according to the general procedure and was obtained in 36% yield (64 mg). White amorphous: R_f = 0.45 (*n*-hexane/EtOAc = 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (t, J = 6.8 Hz, 3H), 1.24−1.29 (m, 5H), 1.43−1.49 (m, 1H), 1.87−2.03 (m, 2H), 2.31 (t, J = 6.8 Hz, 2H), 2.44 (s, 3H), 3.02 (s, 3H), 3.32 (t, J = 6.8 Hz, 2H), 3.58 (s, 1H), 3.78 (s, 3H), 4.20 (d, J = 14.8 Hz, 1H), 4.28 (d, J = 14.8 Hz, 1H), 6.81 (d, J = 8.4 Hz, 2H), 7.06 (t, J = 7.6 Hz, 1H), 7.13 (d, J = 8.4 Hz, 2H), 7.28 (t, J = 7.6 Hz, 1H), 7.32 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 7.6 Hz, 1H), 7.60 (d, J = 7.6 Hz, 1H), 7.73 (d, J = 8.4 Hz, 2H), 9.01 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 19.4, 21.5, 22.5, 24.4, 31.5, 39.7, 43.0, 46.6, 51.9, 55.2, 75.5, 83.6, 84.9, 114.0 (2C), 119.0, 123.2, 127.1 (2C), 127.7, 128.7, 129.0, 129.6 (2C), 129.8 (2C), 130.5, 135.9, 136.5, 143.6, 159.3; IR (ATR) ν 3437, 3213, 2929, 1512, 1331, 1247, 1150, 1092, 969, 814, 734 cm^{-1}; HRMS (ESI-TOF) m/z [M + Na]$^+$ Calcd for $C_{32}H_{40}N_2NaO_6S_2^+$ 635.2220, found 635.2202.

*N-(5-Cyclohexyl-5-hydroxy-5-(2-(methylsulfonamido)phenyl)-pent-3-yn-1-yl)-N-(4-methoxybenzyl)-4-methylbenzenesulfonamide (**5g**).* This compound was synthesized from from the ketone derivative (170 mg, 0.31 mmol) according to the general procedure and was obtained in 30% yield (59 mg). White amorphous: R_f = 0.42 (*n*-hexane/EtOAc = 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02−1.32 (m, 6H), 1.63−1.69 (m, 2H), 1.78−1.85 (m, 2H), 2.01 (m, 1H), 2.31 (t, J = 6.8 Hz, 2H), 2.44 (s, 3H), 3.02 (s, 3H), 3.32 (t, J = 6.8 Hz, 2H), 3.68 (s, 1H), 3.79 (s, 3H), 4.21 (d, J = 15.2 Hz, 1H), 4.29 (d, J = 15.2 Hz, 1H), 6.81 (d, J = 8.8 Hz, 2H), 7.05 (t, J = 7.6 Hz, 1H), 7.16 (d, J = 8.8 Hz, 2H), 7.28 (t, J = 7.6 Hz, 1H), 7.32 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 8.4 Hz, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.72 (d, J = 8.4 Hz, 2H), 9.08 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.4, 21.5, 26.0, 26.0, 26.1, 27.1, 28.3, 39.5, 46.8, 47.5, 52.0, 55.2, 79.5, 82.4, 85.8, 114.0 (2C), 118.8, 122.7, 127.1 (2C), 127.8, 128.8, 129.6 (2C), 129.7, 129.8 (2C), 130.0, 136.0, 136.4, 143.6, 159.3; IR (ATR) ν 3437, 3204, 2930, 1512, 1332, 1247, 1150, 1092, 969, 815, 733 cm^{-1}; HRMS (ESI-TOF) m/z [M + Na]$^+$ Calcd for $C_{33}H_{40}N_2NaO_6S_2^+$ 647.2220, found 647.2223.

General Procedure for the TFA-Promoted Cascade Cyclization. To a stirred solution of **5a** (142.0 mg, 0.262 mmol) in CH_2Cl_2 (9.17 mL) at 0 °C was added TFA (3.93 mL, 1.0 M in CH_2Cl_2, 3.93 mmol). After required time at the same temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$, and extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (SiO_2, *n*-hexane/EtOAc = 2/1) to give 4a-(4-methoxyphenyl)-5-(methylsulfonyl)-2-tosyl-1,2,3,4,4a,5-hexahydrobenzo[*b*][1,6]naphthyridine **6a** (109.8 mg, 80% yield) as white solid: mp 46−47 °C; R_f = 0.46 (*n*-hexane/EtOAc = 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (td, J = 12.4, 2.4 Hz, 1H), 2.43 (s, 3H), 2.71−2.75 (m, 1H), 2.75 (s, 3H), 3.01 (td, J = 12.4, 4.0 Hz, 1H), 3.60−3.66 (m, 1H), 3.67 (s, 3H), 3.85 (dd, J = 15.2, 1.2 Hz, 1H), 4.41 (d, J = 15.2 Hz, 1H), 6.61 (d, J = 8.8 Hz, 2H), 6.72 (s, 1H), 7.00−7.09 (m, 3H), 7.14 (d, J = 8.8 Hz, 2H), 7.20 (d, J = 7.6 Hz, 1H), 7.32 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 35.2, 39.9, 42.8, 49.2, 55.0, 65.4, 113.4 (2C), 124.1, 125.4, 126.9, 127.6 (2C), 128.0, 128.2 (2C), 128.9, 129.4, 129.9 (2C), 131.0, 133.3, 134.7, 135.9, 143.9, 158.9; IR (ATR) ν 1508, 1338, 1252, 1158, 1099, 1028, 960, 836, 736 cm^{-1}; HRMS (ESI-TOF) m/z [M + Na]$^+$ Calcd for $C_{27}H_{28}N_2NaO_5S_2^+$ 547.1332, found 547.1336.

*4-(5-(Methylsulfonyl)-2-tosyl-1,2,3,4,4a,5-hexahydrobenzo[b]-[1,6]naphthyridin-4a-yl)phenol (**6b**).* This compound was synthesized from **5b** (126.1 mg, 0.24 mmol) according to the general procedure and was obtained in 74% yield (90.6 mg). White solid: mp 140−142 °C; R_f = 0.38 (*n*-hexane/EtOAc = 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (td, J = 12.2, 2.2 Hz, 1H), 2.43 (s, 3H), 2.68−2.74 (m, 1H), 2.74 (s, 3H), 2.98 (td, J = 12.2, 4.8 Hz, 1H), 3.58−3.64 (m, 1H), 3.84 (d, J = 15.2 Hz, 1H), 4.38 (d, J = 15.2, Hz, 1H), 5.31 (s, 1H), 6.55 (d, J = 8.4 Hz, 2H), 6.71 (s, 1H), 7.01−7.10 (m, 5H), 7.17 (d, J = 8.0 Hz, 1H), 7.32 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 35.1, 39.9, 42.8, 49.1, 65.4, 115.0

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(2C), 124.2, 125.5, 127.0, 127.6 (2C), 128.1, 128.4 (2C), 128.9, 129.4, 129.9 (2C), 130.9, 133.1, 134.6, 135.8, 144.0, 155.3; IR (ATR) ν 3420, 1510, 1335, 1265, 1154, 1013, 961, 838, 732, 670 cm^{-1}; HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_{26}H_{26}N_2NaO_5S_2^+$ 533.1175, found 533.1191.

*4a-(4-(Benzyloxy)phenyl)-5-(methylsulfonyl)-2-tosyl-1,2,3,4,4a,5-hexahydrobenzo[b][1,6]naphthyridine (**6c**).* This compound was synthesized from **5c** (134.3 mg, 0.217 mmol) according to the general procedure and was obtained in 71% yield (93.0 mg). White solid: mp 95−98 °C; R_f = 0.50 (*n*-hexane/EtOAc = 1/1); ^1H NMR (400 MHz, $CDCl_3$) δ 2.37 (td, J = 12.4, 2.2 Hz, 1H), 2.42 (s, 3H), 2.70−2.76 (m, 1H), 2.75 (s, 3H), 2.98−3.05 (m, 1H), 2.60−2.66 (m, 1H), 3.85 (d, J = 14.8 Hz, 1H), 4.41 (d, J = 14.8 Hz, 1H), 4.89 (s, 2H), 6.69 (d, J = 8.4 Hz, 2H), 6.71 (s, 1H), 7.00−7.10 (m, 3H), 7.15 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.4 Hz, 1H), 7.30−7.35 (m, 7H), 7.66 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 35.2, 39.9, 42.8, 49.2, 65.4, 69.9, 114.3 (2C), 124.2, 125.4, 127.0, 127.5 (2C), 127.6 (2C), 128.0, 128.1, 128.3 (2C), 128.5 (2C), 128.9, 129.4, 129.9 (2C), 131.3, 133.4, 134.7, 135.9, 136.5, 143.9, 158.3; IR (ATR) ν 1605, 1506, 1338, 1244, 1156, 1013, 960, 835, 733, 698, 674 cm^{-1}; HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_{33}H_{32}N_2NaO_5S_2^+$ 623.1645, found 623.1642.

*4a-(4-Methoxy-3-methylphenyl)-5-(methylsulfonyl)-2-tosyl-1,2,3,4,4a,5-hexahydrobenzo[b][1,6]naphthyridine (**6d**).* This compound was synthesized from **5d** (93.0 mg, 0.167 mmol) according to the general procedure and was obtained in 73% yield (66.0 mg). White solid: mp 132−134 °C; R_f = 0.46 (*n*-hexane/EtOAc = 1/1); ^1H NMR (400 MHz, $CDCl_3$) δ 2.05 (s, 3H), 2.32−2.39 (m, 1H), 2.42 (s, 3H), 2.70−2.76 (m, 1H), 2.75 (s, 3H), 2.99 (td, J = 12.0, 4.8 Hz, 1H), 3.60−3.68 (m, 1H), 3.68 (s, 3H), 3.84 (d, J = 14.8 Hz, 1H), 4.42 (d, J = 14.8 Hz, 1H), 6.44 (d, J = 8.0 Hz, 1H), 6.71 (s, 1H), 6.87 (d, J = 8.0 Hz, 1H), 7.00−7.09 (m, 4H), 7.20 (d, J = 8.0 Hz, 1H), 7.31 (d, J = 8.0 Hz, 2H), 7.66 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.3, 21.5, 35.2, 39.9, 42.8, 49.3, 55.1, 65.5, 108.8, 124.1, 125.4, 125.4, 126.6, 126.9, 127.6 (2C), 128.0, 129.0, 129.3, 129.5, 129.8 (2C), 130.4, 133.5, 134.8, 136.0, 143.8, 157.2; IR (ATR) ν 1501, 1338, 1249, 1157, 1100, 1029, 960, 814, 733 cm^{-1}; HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_{28}H_{30}N_2NaO_5S_2^+$ 561.1488, found 561.1496.

*4a-(4-Methoxyphenyl)-10-methyl-5-(methylsulfonyl)-2-tosyl-1,2,3,4,4a,5-hexahydrobenzo[b][1,6]naphthyridine (**6e**).* This compound was synthesized from **5e** (143.0 mg, 0.257 mmol) according to the general procedure and was obtained in 99% yield (137.1 mg). White solid: mp 130−132 °C; R_f = 0.55 (*n*-hexane/EtOAc = 1/1); ^1H NMR (400 MHz, $CDCl_3$, 55 °C) δ 2.22 (s, 3H), 2.43 (s, 3H), 2.45−2.57 (m, 2H), 2.68 (s, 3H), 2.98 (td, J = 13.0, 5.6 Hz, 1H), 3.48−3.53 (m, 1H), 3.65 (s, 3H), 4.33 (s, 2H), 6.54 (d, J = 8.0 Hz, 2H), 6.99−7.09 (m, 4H), 7.19 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 7.67 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 55 °C) δ 13.5, 21.5, 34.1, 39.8, 41.6, 45.0, 55.0, 65.0, 113.3 (2C), 122.8, 127.0, 127.5 (2C), 127.7, 128.1, 128.2, 129.8 (2C), 130.0 (2C), 130.9, 132.0, 132.5, 134.6, 135.2, 143.7, 159.0; IR (ATR) ν 1606, 1507, 1335, 1249, 1155, 1104, 1034, 956, 959, 815, 734, 662 cm^{-1}; HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_{28}H_{30}N_2NaO_5S_2^+$ 561.1488, found 561.1492.

*4a-(4-Methoxyphenyl)-5-(methylsulfonyl)-10-pentyl-2-tosyl-1,2,3,4,4a,5-hexahydrobenzo[b][1,6]naphthyridine (**6f**).* This compound was synthesized from **5f** (152.9 mg, 0.250 mmol) according to the general procedure and was obtained in 70% yield (103.8 mg). White solid: mp 166−169 °C; R_f = 0.56 (*n*-hexane/EtOAc = 1/1); ^1H NMR (400 MHz, $CDCl_3$, 55 °C) δ 0.95 (t, J = 7.6 Hz, 3H), 1.38−1.60 (m, 6H), 2.44 (s, 3H), 2.52−2.59 (m, 3H), 2.61−2.70 (m, 1H), 2.70 (s, 3H), 2.93−3.00 (m, 1H), 3.48 (dd, J = 9.6, 4.0 Hz, 1H), 3.65 (s, 3H), 4.26 (d, J = 16.0 Hz, 1H), 4.45 (d, J = 16.0 Hz, 1H), 6.54 (d, J = 8.8 Hz, 2H), 7.01 (td, J = 8.0, 0.8 Hz, 1H), 7.03−7.14 (m, 3H), 7.20 (dd, J = 8.0, 0.8 Hz, 1H), 7.22 (dd, J = 8.0, 0.8 Hz, 1H), 7.31 (d, J = 8.0 Hz, 2H), 7.68 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 55 °C) δ 13.9, 21.5, 22.4, 27.8, 28.7, 32.3, 33.9, 40.2, 41.5, 44.4, 55.1, 64.7, 113.3 (2C), 122.7, 126.9, 127.5 (2C), 127.7, 128.1, 129.8 (2C), 130.3 (2C), 130.6, 131.0, 132.6, 133.3, 134.8, 135.6, 143.6, 159.0; IR (ATR) ν 2918, 1507, 1336, 1249, 1156, 1104, 1034, 959, 815, 735, 660 cm^{-1}; HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_{32}H_{38}N_2NaO_5S_2^+$ 617.2114, found 617.2128.

*10-Cyclohexyl-4a-(4-methoxyphenyl)-5-(methylsulfonyl)-2-tosyl-1,2,3,4,4a,5-hexahydrobenzo[b][1,6]naphthyridine (**6g**).* This compound was synthesized from **5g** (131.6 mg, 0.210 mmol) according to the general procedure and was obtained in 86% yield (110.0 mg). White solid: mp 103−105 °C; R_f = 0.48 (*n*-hexane/EtOAc = 1/1); ^1H NMR (400 MHz, $CDCl_3$, 55 °C) δ 1.34−1.47 (m, 3H), 1.67−1.96 (m, 7H), 2.44 (s, 3H), 2.52−2.58 (m, 1H), 2.59−2.66 (m, 1H), 2.71 (s, 3H), 2.76−2.80 (m, 1H), 2.86−2.94 (m, 1H), 3.37 (dd, J = 10.0, 5.2 Hz, 1H), 3.66 (s, 3H), 4.10 (d, J = 15.6 Hz, 1H), 4.72 (d, J = 15.6 Hz, 1H), 6.51−6.54 (m, 2H), 6.97 (t, J = 7.6 Hz, 1H), 7.02 (t, J = 7.6 Hz, 1H), 7.11 (br-s, 2H), 7.18 (d, J = 7.6 Hz, 1H), 7.31 (d, J = 7.6 Hz, 1H), 7.32 (d, J = 8.0 Hz, 2H), 7.67 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 55 °C) δ 21.5, 26.1, 27.0, 27.4, 30.3, 31.9, 32.7, 40.1, 40.7, 41.0, 43.9, 55.1, 65.0, 113.3 (2C), 123.8, 126.5, 127.5 (2C), 127.6, 128.0, 129.8 (2C), 130.4 (2C), 132.0, 132.0, 132.0, 135.1, 135.9, 136.7, 143.7, 159.0; IR (ATR) ν 2928, 1507, 1337, 1249, 1155, 1105, 1024, 961, 815, 733 cm^{-1}; HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_{33}H_{38}N_2NaO_5S_2^+$ 629.2114, found 629.2098.

*4a-(4-Methoxyphenyl)-9-methyl-5-(methylsulfonyl)-2-tosyl-1,2,3,4,4a,5-hexahydrobenzo[b][1,6]naphthyridine (**6h**).* This compound was synthesized from **5h** (120.5 mg, 0.216 mmol) according to the general procedure and was obtained in 73% yield (84.8 mg). White solid: mp 120−122 °C; R_f = 0.47 (*n*-hexane/EtOAc = 1/1); ^1H NMR (400 MHz, $CDCl_3$) δ 2.31 (s, 3H), 2.39 (td, J = 12.0, 2.4 Hz, 1H), 2.44 (s, 3H), 2.64 (br-dd, J = 12.0, 2.4 Hz, 1H), 2.76 (s, 3H), 3.02 (td, J = 12.0, 2.8 Hz, 1H), 3.57−3.61 (m, 1H), 3.67 (s, 3H), 3.99 (dd, J = 14.8, 1.6 Hz, 1H), 4.38 (d, J = 14.8 Hz, 1H), 6.61 (d, J = 8.4 Hz, 2H), 6.89−6.95 (m, 3H), 7.04 (dd, J = 7.2, 2.4 Hz, 1H), 7.15 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.67 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.8, 21.6, 34.9, 40.1, 42.7, 49.2, 55.1, 64.6, 113.4 (2C), 121.2, 127.4, 127.5, 127.6 (2C), 127.7, 128.1 (2C), 128.7, 129.9 (2C), 131.2, 133.0, 133.3, 134.8, 135.7, 143.9, 158.9; IR (ATR) ν 1508, 1465, 1339, 1252, 1160, 1033, 962, 819, 735, 668 cm^{-1}; HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_{28}H_{30}N_2NaO_5S_2^+$ 561.1488, found 561.1503.

*8-Chloro-4a-(4-methoxyphenyl)-5-(methylsulfonyl)-2-tosyl-1,2,3,4,4a,5-hexahydrobenzo[b][1,6]naphthyridine (**6i**).* This compound was synthesized from **5i** (55.2 mg, 0.096 mmol) according to the general procedure and was obtained in 77% yield (41.2 mg). White solid: mp 145−146 °C; R_f = 0.49 (*n*-hexane/EtOAc = 1/1); ^1H NMR (400 MHz, $CDCl_3$) δ 2.35 (td, J = 12.6, 2.0 Hz, 1H), 2.43 (s, 3H), 2.71−2.75 (m, 1H), 2.77 (s, 3H), 3.00 (td, J = 12.6, 4.4 Hz, 1H), 3.63−3.66 (m, 1H), 3.68 (s, 3H), 3.86 (d, J = 15.2 Hz, 1H), 4.42 (d, J = 15.2 Hz, 1H), 6.62 (d, J = 8.4 Hz, 2H), 6.66 (s, 1H), 6.99 (d, J = 8.4 Hz, 2H), 7.10−7.14 (m, 3H), 7.32 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 35.1, 40.1, 42.7, 49.1, 55.1, 65.4, 113.5 (2C), 123.1, 125.0, 127.5 (2C), 128.0, 128.1 (2C), 129.9 (2C), 130.2, 130.5, 130.8, 132.5, 133.2, 133.2, 137.7, 144.0, 159.0; IR (ATR) ν 1508, 1338, 1252, 1158, 1027, 961, 803, 733, 659 cm^{-1}; HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_{27}H_{27}ClN_2NaO_5S_2^+$ 581.0942, found 581.0962.

*7-Chloro-4a-(4-methoxyphenyl)-5-(methylsulfonyl)-2-tosyl-1,2,3,4,4a,5-hexahydrobenzo[b][1,6]naphthyridine (**6j**).* This compound was synthesized from **5j** (106.2 mg, 0.184 mmol) according to the general procedure and was obtained in 76% yield (78.2 mg). White solid: mp 184−187 °C; R_f = 0.42 (*n*-hexane/EtOAc = 1/1); ^1H NMR (400 MHz, $CDCl_3$) δ 2.36 (td, J = 12.8, 3.0 Hz, 1H), 2.43 (s, 3H), 2.72−2.77 (m, 1H), 2.77 (s, 3H), 2.98 (td, J = 12.8, 4.8 Hz, 1H), 3.62−3.67 (m, 1H), 3.70 (s, 3H), 3.83 (d, J = 14.8 Hz, 1H), 4.39 (d, J = 14.8 Hz, 1H), 6.64 (d, J = 8.4 Hz, 2H), 6.68 (s, 1H), 6.95 (d, J = 8.0 Hz, 1H), 7.05 (dd, J = 8.0, 2.0 Hz, 1H), 7.12 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 2.0 Hz, 1H), 7.32 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 35.3, 40.2, 42.7, 49.2, 55.1, 65.6, 113.6 (2C), 123.2, 126.2, 127.1, 127.3, 127.6 (2C), 128.2 (2C), 129.2, 129.9 (2C), 130.5, 133.2, 133.2, 135.8, 136.2, 144.0, 159.1; IR (ATR) ν 1596, 1508, 1340, 1253, 1159, 1105, 1027, 960, 817, 735, 666 cm^{-1}; HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_{27}H_{27}ClN_2NaO_5S_2^+$ 581.0942, found 581.0962.

*4a-(4-Methoxyphenyl)-6-methyl-5-(methylsulfonyl)-2-tosyl-1,2,3,4,4a,5-hexahydrobenzo[b][1,6]naphthyridine (**6k**).* This com-

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pound was synthesized from **5k** (108.9 mg, 0.196 mmol) according to the general procedure and was obtained in 61% yield (64.7 mg). White solid: mp 120−121 °C; R_f = 0.46 (*n*-hexane/EtOAc = 1/1); ^{1}H NMR (400 MHz, $CDCl_3$, 55 °C) δ 2.16 (s, 3H), 2.29 (t, J = 12.4 Hz, 1H), 2.41 (s, 3H), 2.66−2.70 (m, 1H), 2.85 (s, 3H), 3.16 (td, J = 13.2, 4.4 Hz, 1H), 3.67 (s, 3H), 3.66−3.70 (m, 1H), 3.79 (d, J = 14.4 Hz, 1H), 4.47 (d, J = 14.4 Hz, 1H), 6.59 (d, J = 8.4 Hz, 2H), 6.69 (s, 1H), 6.84 (d, J = 7.2 Hz, 1H), 6.88 (d, J = 7.6 Hz, 1H), 6.98 (t, J = 8.0 Hz, 1H), 7.10 (br-s, 2H), 7.29 (d, J = 8.0 Hz, 2H), 7.65 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 55 °C) δ 18.9, 21.5, 35.1, 40.6, 43.0, 49.4, 55.1, 65.4, 113.5 (2C), 123.1, 125.1, 127.2, 127.7 (2C), 128.4 (2C), 129.9 (2C), 130.2, 130.3, 130.9, 134.0, 134.1, 136.0, 139.2, 143.8, 159.3; IR (ATR) ν 1508, 1460, 1337, 1252, 1158, 1034, 959, 837, 789, 738, 674 cm^{-1}; HRMS (ESI-TOF) m/z [M + Na]$^+$ Calcd for $C_{28}H_{30}N_2NaO_5S_2^+$ 561.1488, found 561.1508.

*4a-(4-Methoxyphenyl)-2-tosyl-2,3,4,4a-tetrahydro-1H-chromeno[3,2-c]pyridine (**6l**).* This compound was synthesized from **5l** (100.0 mg, 0.214 mmol) according to the general procedure and was obtained in 45% yield (42.8 mg). White solid: mp 159−160 °C; R_f = 0.36 (*n*-hexane/EtOAc = 2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (td, J = 13.2, 2.0 Hz, 1H), 2.39 (s, 3H), 2.53 (td, J = 13.2, 4.0 Hz, 1H), 2.67 (dd, J = 13.2, 4.0 Hz, 1H), 3.28 (d, J = 13.6 Hz, 1H), 3.71 (s, 3H), 3.82 (dd, J = 13.2, 2.0 Hz, 1H), 4.44 (d, J = 13.6 Hz, 1H), 6.56 (s, 1H), 6.57 (d, J = 7.6 Hz, 1H), 6.76 (d, J = 8.8 Hz, 2H), 6.78 (t, J = 7.6 Hz, 1H), 6.96 (d, J = 7.6 Hz, 1H), 6.99 (t, J = 7.6 Hz, 1H), 7.24 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 7.64 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 37.6, 43.4, 50.0, 55.1, 78.7, 113.9 (2C), 116.2, 121.3, 121.6, 122.8, 126.3, 127.6 (2C), 128.2 (2C), 129.4, 129.8 (2C), 129.9, 130.4, 133.6, 143.7, 152.1, 159.4; IR (ATR) ν 1605, 1509, 1348, 1242, 1163, 1029, 958, 832, 746, 662 cm^{-1}; HRMS (ESI-TOF) m/z [M + Na]$^+$ Calcd for $C_{26}H_{25}NNaO_4S^+$ 470.1397, found 470.1390.

*4a-(4-Methoxyphenyl)-10-methyl-2-tosyl-2,3,4,4a-tetrahydro-1H-chromeno[3,2-c]pyridine (**6m**).* This compound was synthesized from **5m** (100.0 mg, 0.208 mmol) according to the general procedure and was obtained in 69% yield (66.9 mg). White solid: mp 170−174 °C; R_f = 0.42 (*n*-hexane/EtOAc = 2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.16 (s, 3H), 2.39 (s, 3H), 2.47−2.56 (m, 3H), 3.26 (d, J = 14.8 Hz, 1H), 3.69 (s, 3H), 3.73−3.77 (m, 1H), 4.86 (d, J = 14.8 Hz, 1H), 6.62 (d, J = 8.0 Hz, 1H), 6.70 (d, J = 8.8 Hz, 2H), 6.82 (t, J = 7.6 Hz, 1H), 7.00 (t, J = 7.6 Hz, 1H), 7.15 (d, J = 7.6 Hz, 1H), 7.15 (d, J = 8.8 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.0, 21.5, 37.7, 42.6, 45.5, 55.1, 78.2, 113.6 (2C), 116.5, 121.2, 123.8, 124.3, 124.9, 126.9, 127.4 (2C), 128.2 (2C), 129.0, 129.7 (2C), 131.6, 134.0, 143.6, 151.8, 159.1; IR (ATR) ν 1604, 1509, 1350, 1248, 1162, 1032, 972, 815, 735, 660 cm^{-1}; HRMS (ESI-TOF) m/z [M + Na]$^+$ Calcd for $C_{27}H_{27}NNaO_4S^+$ 484.1553, found 484.1556.

General Procedure for the Silver Acetate-Catalyzed Hydroamination−TFA-Promoted Skeletal Rearrangement Cascade. To a stirred solution of **5b** (141.3 mg, 0.267 mmol) in CH_3CN (13.4 mL) at room temperature was added AgOAc (4.5 mg, 0.027 μmol). After being stirred for required time at the same temperature, the reaction mixture was concentrated in vacuo. TFA (2.14 mL, 1.0 M in CH_2Cl_2, 2.14 mmol) was added to a stirred solution of the crude product in CH_2Cl_2 (10.7 mL) at 0 °C. After required time, the reaction mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography (SiO_2, *n*-hexane/EtOAc = 2.5/1) to give 4-(6-(methylsulfonyl)-2-tosyl-1,2,3,4,5,6-hexahydroazepino-[4,3-*b*]indol-5-yl)phenol **9b** (121.6 mg, 89% yield) as white solid: mp >200 °C; R_f = 0.37 (*n*-hexane/EtOAc = 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.15−2.21 (m, 1H), 2.36 (s, 3H), 2.38−2.44 (m, 1H), 2.46 (s, 3H), 3.25−3.29 (m, 1H), 3.38 (td, J = 12.2, 3.2 Hz, 1H), 4.48 (d, J = 16.0 Hz, 1H), 4.77 (d, J = 16.0 Hz, 1H), 5.09 (br-s, 1H), 5,15−5.17 (m, 1H), 6.71 (d, J = 8.8 Hz, 2H), 7.01 (d, J = 8.8 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 7.29−7.35 (m, 2H), 7.58−7.61(m, 1H), 7.61 (d, J = 8.0 Hz, 2H), 7.94 (dd, J = 6.4, 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 33.0, 40.7, 40.7, 41.4, 45.1, 114.3, 115.6 (2C), 128.2, 118.6, 123.6, 124.9, 127.3 (2C), 128.1, 129.7 (2C), 130.0 (2C), 132.1, 135.6, 136.0, 139.4, 143.5, 154.9; IR (ATR) ν 3455, 1512, 1455, 1361, 1328, 1149, 974, 815, 760, 669 cm^{-1}; HRMS (ESI-TOF) m/z [M + Na]$^+$ Calcd for $C_{26}H_{26}N_2NaO_5S_2^+$ 533.1175, found 533.1198.

*5-(4-(Benzyloxy)phenyl)-6-(methylsulfonyl)-2-tosyl-1,2,3,4,5,6-hexahydroazepino[4,3-b]indole (**9c**).* This compound was synthesized from **5c** (51.4 mg, 0.083 mmol) according to the general procedure and was obtained in 76% yield (37.7 mg). White solid: mp 112−114 °C; R_f = 0.35 (*n*-hexane/EtOAc = 2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.17−2.21 (m, 1H), 2.38 (s, 3H), 2.38 (s, 3H), 2.38−2.45 (m, 1H), 3.22−3.26 (m, 1H), 3.36−3.42 (m, 1H), 4.44 (d, J = 16.0 Hz, 1H), 4.82 (d, J = 16.0 Hz, 1H), 4.99 (d, J = 12.0 Hz, 1H), 5.03 (d, J = 12.0 Hz, 1H), 5.17 (dd, J = 6.4, 3.2 Hz, 1H), 6.89 (d, J = 8.4 Hz, 2H), 7.11 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 7.28−7.40 (m, 7H), 7.61−7.64 (m, 3H), 7.94 (dd, J = 6.8, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 32.7, 40.5, 40.5, 41.3, 44.9, 69.9, 114.1, 114.9 (2C), 118.1, 118.3, 123.5, 124.8, 127.2 (2C), 127.5 (2C), 127.9, 127.9, 128.5 (2C), 129.6 (2C), 129.9 (2C), 132.1, 135.0, 135.7, 136.7, 139.3, 143.4, 157.7; IR (ATR) ν 1508, 1454, 1363, 1240, 1154, 974, 829, 732, 665 cm^{-1}; HRMS (ESI-TOF) m/z [M + Na]$^+$ Calcd for $C_{33}H_{32}N_2NaO_5S_2^+$ 623.1645, found 623.1620.

*5-(4-(Benzyloxy)phenyl)-10-methyl-6-(methylsulfonyl)-2-tosyl-1,2,3,4,5,6-hexahydroazepino[4,3-b]indole (**9h**).* This compound was synthesized from **5h** (82.8 mg, 0.149 mmol) according to the general procedure and was obtained in 80% yield (64.0 mg). White solid: mp >200 °C; R_f = 0.32 (*n*-hexane/EtOAc = 2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.17−2.24 (m, 1H), 2.32−2.41 (m, 1H), 2.40 (s, 3H), 2.47 (s, 3H), 2.84 (s, 3H), 3.09−3.14 (m, 1H), 3.37 (td, J = 12.0, 3.6 Hz, 1H), 3.77 (s, 3H), 4.46 (d, J = 16.4 Hz, 1H), 5.20−5.24 (m, 1H), 5.26 (d, J = 16.4 Hz, 1H), 6.83 (d, J = 8.0 Hz, 2H), 7.07 (d, J = 7.2 Hz, 1H), 7.18 (d, J = 8.0 Hz, 2H), 7.19 (t, J = 7.2 Hz, 1H), 7.25 (d, J = 6.8 Hz, 2H), 7.61 (d, J = 6.8 Hz, 2H), 7.85 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 21.5, 32.2, 40.5, 40.9, 41.7, 45.0, 55.1, 112.0, 113.8 (2C), 120.0, 124.4, 126.1, 126.3, 127.1 (2C), 129.7 (2C), 129.9 (2C), 130.2, 131.7, 134.9, 136.1, 139.2, 143.4, 158.5; IR (ATR) ν 1509, 1337, 1247, 1154, 1109, 1025, 958, 835, 738, 665 cm^{-1}; HRMS (ESI-TOF) m/z [M + Na]$^+$ Calcd for $C_{28}H_{30}N_2NaO_5S_2^+$ 561.1488, found 561.1511.

*5-(4-(Benzyloxy)phenyl)-8-chloro-6-(methylsulfonyl)-2-tosyl-1,2,3,4,5,6-hexahydroazepino[4,3-b]indole (**9j**).* This compound was synthesized from **5j** (39 mg, 0.068 mmol) according to the general procedure and was obtained in 74% yield (28 mg). White solid: mp 85−86 °C; R_f = 0.26 (*n*-hexane/EtOAc = 2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.15−2.22 (m, 1H), 2.38−2.47 (m, 1H), 2.40 (s, 3H), 2.44 (s, 3H), 3.17−3.25 (m, 1H), 3.38 (td, J = 12.0, 3.6 Hz, 1H), 3.77 (s, 3H), 4.38 (d, J = 16.0 Hz, 1H), 4.80 (d, J = 16.0 Hz, 1H), 5.15 (dd, J = 6.8, 3.2 Hz, 1H), 6.83 (d, J = 8.4 Hz, 2H), 7.11 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 7.33 (dd, J = 8.4, 1.6 Hz, 1H), 7.53 (d, J = 8.4 Hz, 1H), 7.63 (d, J = 8.0 Hz, 2H), 7.98 (d, J = 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 32.7, 40.4, 40.9, 41.3, 44.8, 55.2, 114.0 (2C), 114.4, 118.1, 118.9, 124.1, 126.3, 127.2 (2C), 129.7 (2C), 129.9 (2C), 130.8, 131.4, 135.0, 135.9, 140.0, 143.6, 158.7; IR (ATR) ν 1509, 1365, 1247, 1158, 1110, 1032, 979, 812, 736, 664 cm^{-1}; HRMS (ESI-TOF) m/z [M + Na]$^+$ Calcd for $C_{27}H_{27}ClN_2NaO_5S_2^+$ 581.0942, found 581.0954.

*5-(4-Methoxyphenyl)-2-tosyl-2,3,4,5-tetrahydro-1H-benzofuro-[3,2-c]azepine (**9l**).* This compound was synthesized from **5l** (102.7 mg, 0.22 mmol) according to the general procedure and was obtained in 66% yield (65.4 mg). White solid: mp 58−60 °C; R_f = 0.44 (*n*-hexane/EtOAc = 2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.16−2.24 (m, 1H), 2.33−2.39 (m, 1H), 2.37 (s, 3H), 3.38 (ddd, J = 13.6, 9.2, 2.0 Hz, 1H), 3.59 (ddd, J = 13.6, 6.8, 2.0 Hz, 1H), 3.76 (s, 3H), 4.29−4.34 (m, 1H), 4.46 (d, J = 16.0 Hz, 1H), 4.89 (d, J = 16.0 Hz, 1H), 6.80 (d, J = 8.0 Hz, 2H), 6.93 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 8.4 Hz, 2H), 7.23−7.28 (m, 2H), 7.29 (td, J = 6.8, 2.4 Hz, 1H), 7.53 (dd, J = 6.8, 2.4 Hz, 1H), 7.64 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 33.8, 41.6, 43.4, 45.9, 55.2, 111.1, 113.9, 114.0 (2C), 118.4, 122.6, 124.0, 127.1 (2C), 127.8, 128.8 (2C), 129.6 (2C), 132.7, 135.8, 143.3, 153.7, 155.7, 158.4; IR (ATR) ν 1509, 1454, 1339, 1247, 1157, 1091, 1032, 812, 740 cm^{-1}; HRMS (ESI-TOF) m/z [M + Na]$^+$ Calcd for $C_{26}H_{25}NNaO_4S^+$ 470.1397, found 470.1390.

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■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR charts of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Tel/Fax: 81-43-226-2920. E-mail: y-hamada@faculty.chiba-u.jp.

Notes

The authors declare no competing financial interest.

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