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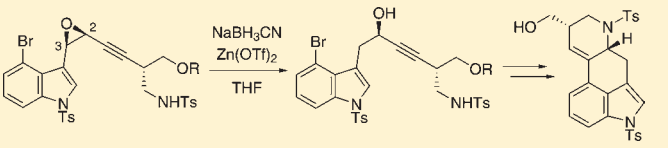
Formal Total Synthesis of (+)-Lysergic Acid via Zinc(II)-Mediated Regioselective Ring-Opening Reduction of 2-Alkynyl-3-indolyloxirane

Akira Iwata, Shinsuke Inuki, Shinya Oishi, Nobutaka Fujii,* and Hiroaki Ohno*

Graduate School of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan

Supporting Information

ABSTRACT: Asymmetric formal synthesis of (+)-lysergic acid was achieved with a reductive ring-opening reaction of chiral 2-alkynyl-3-indolyloxirane with $NaBH_3CN$ as the key step. With $Zn(OTf)_2$ as an additive, the ring-opening reaction proceeded regioselectively at the 3-position to give the corresponding propargyl alcohol, which was a precursor of the allenic amide for palladium-catalyzed domino cyclization to construct the ergot alkaloid core structure.



The family of ergot alkaloids produced by the fungus *Claviceps purpurea* is one of the most intriguing classes of natural products because of their broad biological and pharmacological activities.[1,2] Furthermore, their synthetic derivatives, such as pergolide or bromocriptine, are used clinically as antiprolactin and anti-Parkinson's disease drugs. Ergot alkaloids, particularly lysergic acid, have a unique tetracyclic skeleton containing a [*cd*]-fused indole, $\Delta^{9,10}$-double bond and chiral centers at C5 and C8. The biological importance and structural features of ergot alkaloids have stimulated research in the synthetic community, and a number of total syntheses have been reported to date.[3] However, the only enantioselective syntheses of lysergic acid (**1**) have been by Szántay in 2004[4] and Fukuyama in 2009 (Figure 1).[5,6]

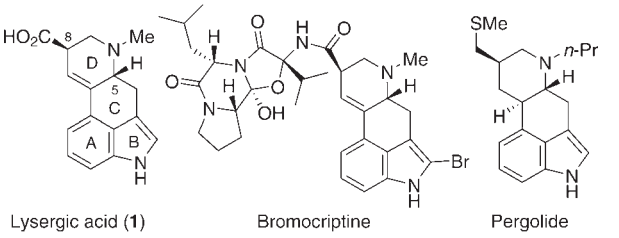


Figure 1. Indole alkaloids of the ergot family and synthetic derivatives.

Recently, we reported the enantioselective total syntheses of (+)-lysergic acid (**1**) and related ergot alkaloids using a palladium-catalyzed domino cyclization of chiral allenic tosylamides **3** bearing a bromoindolyl group (Scheme 1).[7] This domino reaction directly provides the tetracyclic indole **2**, which is a common intermediate for ergot alkaloid synthesis. In this synthetic route, the requisite allenic tosylamide **3** for the domino cyclization was prepared by method of Myers from the propargyl alcohol **4**,[8] which in turn was obtained by the Nozaki–Hiyama–Kishi (NHK) reaction of an indolylacetaldehyde derivative with an iodoalkyne. The stereogenic center of **4** at the propargylic position, which was required for chiral allene formation, was created by a two-step Dess–Martin oxidation and (*R*)-Alpine-borane reduction.

In this study, a novel synthesis of the allenic tosylamide **3** was planned by reductive ring-opening reaction of the chiral oxirane **5**. This new synthetic route omits the redundant oxidation–asymmetric reduction sequence of the previous synthesis. The challenge was to control the regioselectivity of the ring-opening reaction because 2-alkynyloxirane **5** bearing an indolyl group at the 3-position has three reactive carbons, which are A (S_N2 at the indolyl position),[9] B (S_N2 at the propargylic position),[10] and C (S_N2')[11] (Scheme 1).[12] Because the reductive ring-opening reaction of indolyl-substituted alkynyloxiranes is unprecedented, no information was available for appropriate reaction conditions to control the regio- and stereoselectivities. Herein we describe a regioselective reductive ring-opening reaction of alkynyloxirane **5** with $NaBH_3CN$ in the presence of $Zn(OTf)_2$ and the asymmetric formal total synthesis of lysergic acid. Mechanistic consideration of the reaction is also presented.

Retrosynthetic analysis of the tetracyclic indole **2** is illustrated in Scheme 1. The chiral propargyl alcohol **4**, which is the precursor of the allenic amide **3** for stereoselective construction of **2**, will be obtained by regioselective reduction of the oxirane **5** via path A. Oxirane **5** can be prepared by asymmetric/stereoselective epoxidation of enyne **6**. It is well-known that (*E*)-enynes generally show sufficient asymmetric induction in Shi's asymmetric epoxidation.[13] However, our preliminary investigation showed that stereoselective preparation of the (*E*)-enyne was difficult in this case.[14] Therefore, we planned to prepare enyne **6** with a (*Z*)-configuration by a cross-coupling reaction between vinyl bromide **7** and the known enantiopure alkyne **8**.[7] Stereoselective preparation of (*Z*)-vinyl bromide **7** would be achieved by Uenishi's method.[15]

The synthesis was started from commercially available 4-bromoindole **9** (Scheme 2). According to the literature procedure,[16]

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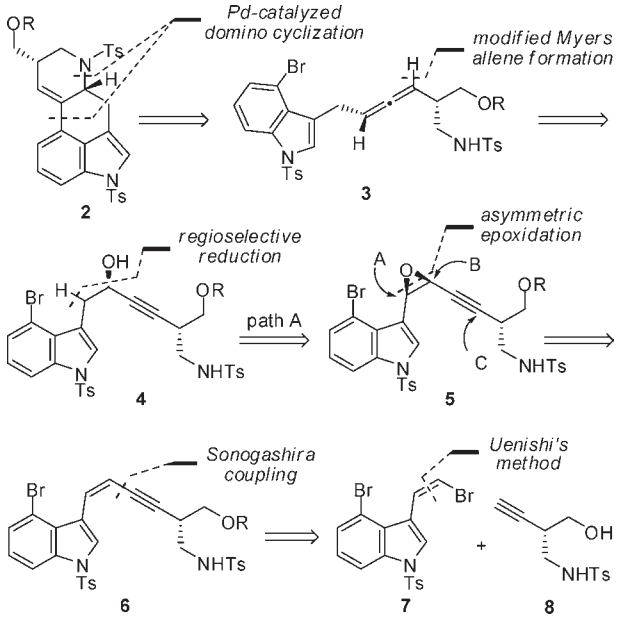
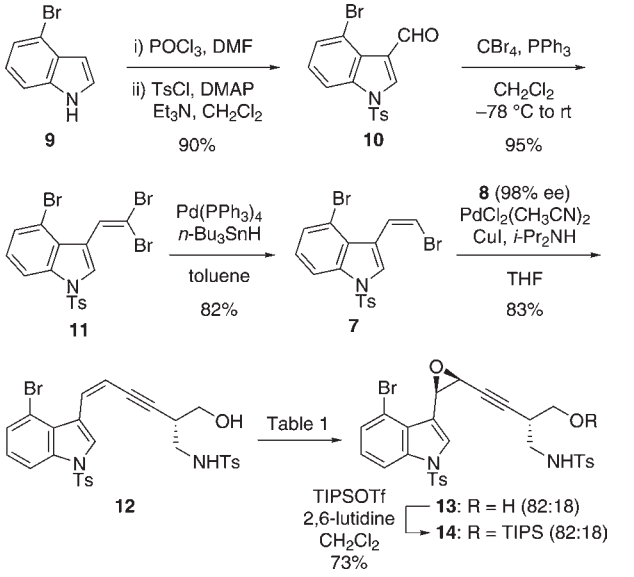
Scheme 1. Retrosynthetic Analysis of the Tetracyclic Indole 2



Scheme 2. Synthesis of 2-Alkynyl-3-indolyloxirane 14

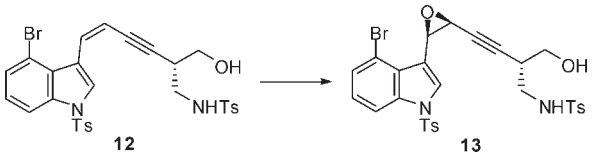


Vilsmeier–Haack reaction of **9** followed by protection of the indole nitrogen gave aldehyde **10**. Treatment of aldehyde **10** with CBr_4 and PPh_3 followed by palladium-catalyzed selective hydrogenolysis of the bromo group at the trans position with Bu_3SnH (Uenishi's method)[15] gave the (*Z*)-vinyl bromide **7** in good yield. The existence of the bromo substituent at the indole 4 position was not problematic. Sonogashira coupling of **7** with the known alkyne **8** (98% ee), prepared by the same five-step sequence from (*S*)-Garner's aldehyde via palladium/indium-mediated reductive coupling of an ethynylaziridine with formaldehyde,[17] afforded (*Z*)-enyne **12**, which is the precursor of the alkynyloxirane.

Next, asymmetric epoxidation of enyne **12** was investigated (Table 1). The reaction of **12** with Shi's catalyst **15** under the established conditions[18] at 0 °C provided the desired chiral oxirane **13** in a low yield (35%, dr = 82:18, entry 1). Considering the poor solubility of enyne **12**, the volume of solvent in the reaction and the amount of the reagents (*n*-Bu_4NHSO_4 and Oxone) were increased to obtain **13** in 77% yield (dr = 82:18, entry 2). Decreasing the temperature of the reaction (−10 °C) slightly decreased the yield (62%, dr = 82:18, entry 3). Unfortunately, Shi's ketone **16**,[19] which is widely used as a catalyst for asymmetric epoxidation of (*Z*)-alkenes, was not effective in this case (25% yield, dr = 50:50, entry 4). It should be noted that epoxidation using *m*-CPBA was not successful and led to decomposition of the substrate **12** (entry 5). When the 82:18 diastereomixture **13** obtained in entry 2 (the ratio determined by ^1H NMR and HPLC analysis) was used, the oxirane **14** for the ring-opening reaction was prepared by silylation with TIPSOTf (Scheme 2).

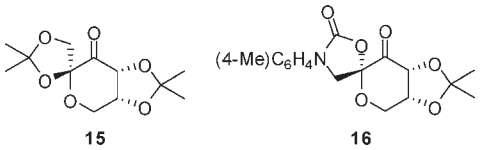
The reductive ring-opening reaction was then investigated using an 82:18 diastereomixture of **14** because of the difficulty in separating each of the diastereomers resulting from epoxidation. Reaction of oxirane **14** with various reducing agents such as $NaBH_4$ and DIBAL gave a complex mixture of unidentified products without producing the desired propargyl alcohol **17**. Oxirane **14** was inert to $NaBH_3CN$ reduction leading to 79% recovery of the starting material (Table 1, entry 1). We then turned our attention to the Lewis acid-mediated reaction based on the known reductive ring-opening reaction of oxiranes[20] including 2,3-diaryl-substituted ones.[21] We expected that an oxophilic Lewis acid would facilitate regioselective ring cleavage of the oxirane at the 3-position with the assistance of the electron-donating indole ring and produce the desired product **17** by hydride reduction of the resulting indolium intermediate.

Table 1. Epoxidation of Enyne 12[a]



		oxidant					
entry	chiral cat.	Oxone (equiv)	*n*-Bu_4NHSO_4 (equiv)	temp (°C)	yield[b] (%)	recov (%)	dr[c]
1	**15**	2	0.04	0	35	48	82:18
2	**15**	3	0.4	0	77	17	82:18
3	**15**	3	0.4	−10	62	30	82:18
4	**16**	3	0.4	0	25	34	50:50
5	*m*-CPBA (3 equiv)			rt	ND[d]		

[a] The reactions were carried out with a substrate concentration of 100 mM (entry 1) or 50 mM (entries 2–4), chiral catalyst **15** or **16** (50 mol %), Oxone in aqueous $Na_2(EDTA)$ (4×10^{-4} M), 1.47 M aqueous KOH and *n*-Bu_4NHSO_4 in CH_3CN–DMM and K_2CO_3–AcOH buffer. [b] Isolated yield. [c] Determined by ^1H NMR analysis. [d] ND = Not detected. Oxone = $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$; DMM = dimethoxymethane.



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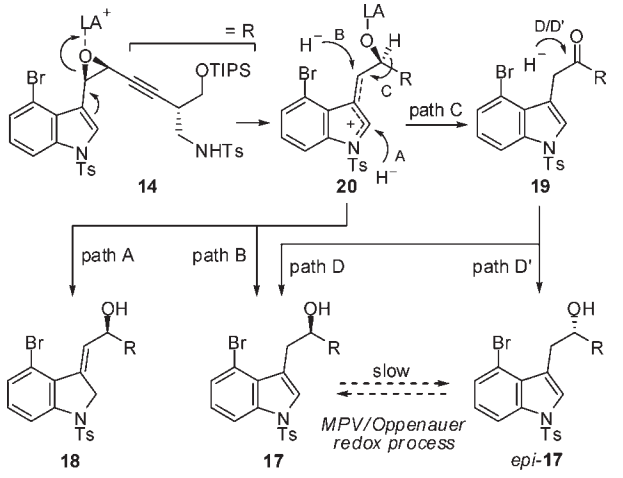
Among the several Lewis acids investigated, Me_2AlCl showed clean conversion to produce **17** regioselectively in 87% yield. However, the propargylic position was almost completely epimerized (dr = 48:52, entry 4). Fortunately, use of $ZnCl_2$ provided the desired alcohol **17** in 49% yield with only a slight decrease in the diastereomeric ratio (78:22, entry 5). Further screening of other zinc(II) salts (entries 6−9) revealed that $Zn(OTf)_2$ was the most effective and produced alcohol **17** in 55% yield without promoting any epimerization at the propargylic position (dr = 82:18, entry 8). In all cases examined, neither the S_N2 product at the 2-position nor S_N2' product was isolated. By contrast, formation of the double bond isomer **18** and/or the ketone **19** occurred (entries 5−9).

A rationale for the observed results of the reductive ring-opening reaction is depicted in Scheme 3. Lewis acid activation of the oxirane **14** induces formation of the indolium intermediate **20**. Isolation of the double bond isomer **18**, which would be produced by hydride reduction of **20** at the indole 2 position (path A), partly supports the intermediacy of **20** in this reaction. The desired alcohol **17**, the major product in the $Zn(OTf)_2$-mediated reduction, results from hydride reduction at the indolyl position (path B). Alternatively, a 1,2-hydride shift from **20** (path C) followed by reduction of the resulting ketone **19** (path D and D′) under the reductive conditions can explain the formation of **17** that accompanies complete epimerization when using Me_2AlCl (entry 4). As shown in entry 8 (Table 2), the $Zn(OTf)_2$-mediated reaction stereoselectively produced the desired product **17** and a considerable amount of the ketone **19**. This result suggests that the activation ability of $Zn(OTf)_2$ toward ketone reduction (path D and D′) is relatively low compared to that of Me_2AlCl.

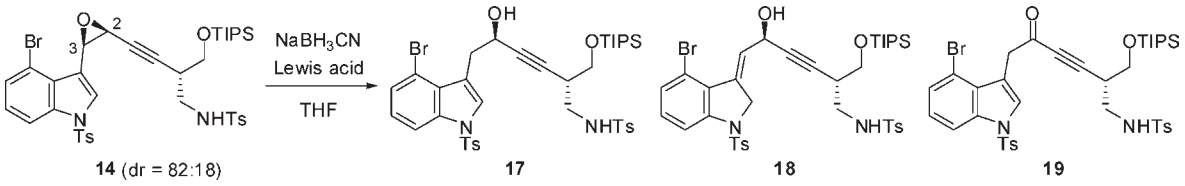
Scheme 3. Pathways for the Reductive Ring-Opening Reaction



The above discussions were supported by the following experiments (Scheme 4). On treatment of ketone **19** under the $Zn(OTf)_2$-mediated reduction conditions [$NaBH_3CN$, $Zn(OTf)_2$ in THF at 60 °C], formation of the alcohols **17** and *epi*-**17** was not observed (eq 1). The reaction of ketone **19** under the Me_2AlCl-mediated reduction conditions afforded the alcohols **17** and *epi*-**17** in an almost 1:1 diastereomixture (eq 2). Furthermore, reaction of **17** (dr = 78:22) in the presence of **19** (1 equiv) with $NaBH_3CN$ and Me_2AlCl gave a 62:38 diastereomixture of **17** (eq 3), which was the predicted ratio considering the reduction of **19**. This confirmed that the Meerwein−Ponndorf−Verley (MPV)/Oppenauer redox process[22] between **17** and **19** was not the major pathway for epimerization in the presence of Me_2AlCl (Table 2, entry 4). In the absence of $NaBH_3CN$, no epimerization of **17** was observed in the reaction after 2 h (eq 4).[23]

Finally, the asymmetric formal total synthesis of (+)-lysergic acid (**1**) was completed in two steps from the propargyl alcohol **17** (dr = 82:18) (Scheme 5). The alcohol **17** was stereoselectively transformed into the allene **3a** using the modified procedure for Myers allene formation.[24] Subsequent cleavage of the silyl group of **3a** gave the known allenic tosylamide **3b** (dr = 82:18).[7] As we previously reported, the tetracyclic indole **2a** was

Table 2. Reductive Ring-Opening Reaction of 2-Alkynyl-3-indolyloxirane 14[a]



14 (dr = 82:18) 17 18 19

entry	Lewis acid	temp (°C)	time (h)	yield (%) 17[b] (dr)[c]	18[b]	19[d]	recov (%)
1	none	rt	2				79
2	$Sm(OTf)_3$	40	28	16 (57:43)		43	
3	$In(OTf)_3$	60	0.5	13 (79:21)	2	34	
4	Me_2AlCl	60	0.25	87 (48:52)			
5	$ZnCl_2$	60	2.5	49 (78:22)	10	7	
6	$ZnBr_2$	60	2	22 (80:20)	10	15	52
7	ZnI_2	60	2	22 (70:30)		47	
8	$Zn(OTf)_2$	60	2	55 (82:18)	trace	20	
9[e]	$Zn(OTf)_2$	100	0.5	45 (78:22)		52	

[a] The reactions were carried out with substrate **14**, $NaBH_3CN$ (3 equiv), and Lewis acid (3 equiv) in THF. [b] Calculated from the combined isolated yields (**17** and **18**) and HPLC analysis (Chiralcel OD-H). [c] Determined by HPLC analysis (Chiralcel OD-H). [d] Isolated yields. [e] Reaction was carried out in dioxane.

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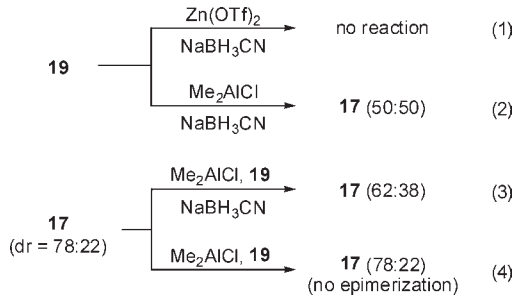
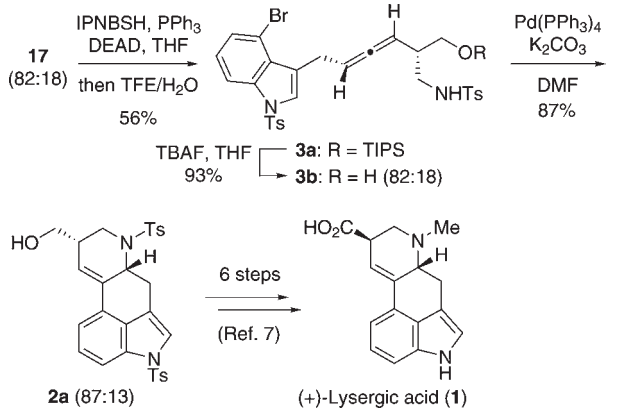
Scheme 4. Supporting Experiments for the Proposed Reaction Pathways



Scheme 5. Formal Total Synthesis of Lysergic Acid[a]



[a] Abbreviations: IPNBSH = *N*-isopropylidene-*N*′-2-nitrobenzenesulfonyl hydrazine; TFE = trifluoroethanol.

obtained from **3b** in 87% yield with an 87:13 selectivity via the palladium-catalyzed domino cyclization of the allenic tosylamide **3b**. The reported six-step sequence of reactions, including separation of the diastereomers after oxidation and esterification, would provide (+)-lysergic acid (**1**).

In summary, a novel method for regio- and stereoselective construction of propargyl alcohol was developed based on a regioselective ring-opening reaction of 2-alkynyl-3-indolyloxirane at the 3-position. Addition of $Zn(OTf)_2$ was important for promotion of the oxirane cleavage at the 3-position and suppression of epimerization at the propargylic position. With this reduction as the key step, asymmetric formal total synthesis of (+)-lysergic acid was achieved.

EXPERIMENTAL SECTION

General Methods. All moisture-sensitive reactions were performed using syringe-septum cap techniques under an argon atmosphere, and all glassware was dried in an oven at 80 °C for 2 h prior to use. Reactions at −78 °C employed a CO_2−MeOH bath. Melting points were measured by a hot-stage melting point apparatus (uncorrected). Chemical shifts are reported in δ (ppm) relative to TMS in $CDCl_3$ as internal standard (^{1}H NMR) or the residual $CHCl_3$ signal (^{13}C NMR). ^{1}H NMR spectra are tabulated as follows: chemical shift, multiplicity (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), number of protons, and coupling constant(s). The compounds **8**[7] and **10**[25] were synthesized according to the reported procedures.

4-Bromo-3-(2,2-dibromovinyl)-1-tosyl-1*H*-indole (11). To a stirred mixture of PPh_3 (25.0 g, 95.4 mmol) in CH_2Cl_2 (100 mL) was added CBr_4 (15.8 g, 47.7 mmol) at −20 °C under argon. After the mixture was stirred for 15 min at this temperature, a solution of aldehyde **10** (6.00 g, 15.9 mmol) in CH_2Cl_2 (40 mL) was added at −78 °C. After being stirred for 10 min at this temperature, the mixture was allowed to warm to room temperature and stirred for a further 2.5 h at this temperature. Concentration under reduced pressure gave an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane−EtOAc (4:1) to give **11** as a pale yellow solid (7.66 g, 95% yield). Recrystallization from *n*-hexane−EtOAc gave pure **11** as colorless crystals: mp 152−153 °C; IR (neat) 1368 (NSO_2), 1163 (NSO_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 3H), 7.15 (dd, J = 8.0, 8.0 Hz, 1H), 7.25 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.0 Hz, 1H), 7.76 (d, J = 8.0 Hz, 2H), 7.96 (d, J = 8.0 Hz, 1H), 8.10 (d, J = 1.0 Hz, 1H), 8.11 (d, J = 1.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 90.5, 112.9, 114.2, 117.9, 125.9, 126.9, 127.0 (2C), 127.4, 128.3, 128.8, 130.1 (2C), 134.5, 135.4, 145.7. Anal. Calcd for $C_{17}H_{12}Br_3NO_2S$: C, 38.23; H, 2.26; N, 2.62. Found: C, 38.03; H, 2.17; N, 2.50.

(*Z*)-4-Bromo-3-(2-bromovinyl)-1-tosyl-1*H*-indole (7). To a stirred mixture of **11** (1.50 g, 2.81 mmol) in toluene (28 mL) were added $Pd(PPh_3)_4$ (130 mg, 0.110 mmol; 4 mol %) and Bu_3SnH (0.831 mL, 3.09 mmol) at room temperature under argon, and the mixture was stirred for 8.5 h at this temperature. The mixture was concentrated under reduced pressure to give a yellow oil, which was purified by flash chromatography over silica gel with *n*-hexane−EtOAc (20:1) to give **7** as a white solid. Recrystallization from *n*-hexane−$CHCl_3$ gave pure **7** (1.05 g, 82%) as colorless crystals: mp 136−137 °C; IR (neat) 1373 (NSO_2), 1172 (NSO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.34 (s, 3H), 6.54 (d, J = 7.4 Hz, 1H), 7.14 (dd, J = 8.0, 8.0 Hz, 1H), 7.24 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 8.0 Hz, 2H), 7.87 (d, J = 7.4 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H), 8.35 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 107.5, 112.8, 114.3, 116.9, 124.1, 125.6, 127.0 (2C), 127.2, 127.8, 128.3, 130.0 (2C), 134.6, 135.5, 145.5. Anal. Calcd for $C_{17}H_{13}Br_2NO_2S$: C, 44.86; H, 2.88; N, 3.08. Found: C, 44.73; H, 3.00; N, 2.98.

(*S,Z*)-*N*-[6-(4-Bromo-1-tosyl-1*H*-indol-3-yl)-2-(hydroxymethyl)hex-5-en-3-yn-1-yl]-4-methylbenzenesulfonamide (12). To a stirred mixture of **7** (800 mg, 1.76 mmol) in a mixed solvent of $(i\text{-Pr})_2NH$ (16 mL) and THF (16 mL) were added **8** (608 mg, 2.40 mmol), $PdCl_2(CH_3CN)_2$ (22.9 mg, 0.0883 mmol), and CuI (33.6 mg, 0.176 mmol) at room temperature under argon, and the mixture was stirred for 3 h at this temperature. The mixture was concentrated under reduced pressure to give a yellow amorphous solid, which was purified by flash chromatography over silica gel with *n*-hexane−EtOAc (2:1) to give **12** as a yellow amorphous solid (913 mg, 83% yield): $[\alpha]^{29}_D$ −41.7 (*c* 0.59, $CHCl_3$); IR (neat) 3323 (OH), 2248 (C≡C), 1415 (NSO_2), 1372 (NSO_2), 1173 (NSO_2), 1157 (NSO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.36 (s, 3H), 2.40 (s, 3H), 2.59 (dd, J = 6.3, 6.3 Hz, 1H), 3.03−3.09 (m, 1H), 3.25−3.36 (m, 2H), 3.85−3.96 (m, 2H), 5.20 (dd, J = 6.7, 6.7 Hz, 1H), 5.71 (dd, J = 11.7, 2.1 Hz, 1H), 7.14 (dd, J = 8.0, 8.0 Hz, 1H), 7.27 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 7.42 (d, J = 8.0 Hz, 1H), 7.66 (d, J = 11.7 Hz, 1H), 7.77−7.81 (m, 4H), 7.94 (d, J = 8.0 Hz, 1H), 8.66 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 21.6, 36.4, 43.4, 62.3, 83.2, 95.4, 106.3, 112.7, 114.5, 118.9, 125.5, 126.8, 127.0 (2C), 127.1 (2C), 127.5, 128.5, 129.3, 129.8 (2C), 130.2 (2C), 134.4, 135.5, 136.8, 143.6, 145.8. Anal. Calcd for $C_{29}H_{27}BrN_2O_5S_2$: C, 55.50; H, 4.34; N, 4.46. Found: C, 55.37; H, 4.46; N, 4.26.

***N*-[(*S*)-4-[(2*S*,3*R*)-(4-Bromo-1-tosyl-1*H*-indol-3-yl)oxiran-2-yl]-2-(hydroxymethyl)but-3-yn-1-yl]-4-methylbenzenesulfonamide (13).** All glassware used for the epoxidation reaction was carefully washed and coated with 0.1 M potassium hydroxide

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2-propanolic solution. To a stirred mixture of **12** (50 mg, 0.080 mmol), the chiral ketone **15** (10.3 mg, 0.040 mmol), and *n*-Bu_4NHSO_4 (11 mg, 0.032 mmol) in CH_3CN/DMM (1.6 mL, 1:2) was added buffer solution (0.1 M K_2CO_3−AcOH in water; 800 μL) at room temperature under argon. After the mixture was cooled to 0 °C, solutions of Oxone (147.6 mg, 0.24 mmol) in 4×10^{-4} M aqueous Na_2(EDTA) (480 μL) and 1.47 M aqueous KOH (408 μL) were added dropwise to the reaction mixture separately and simultaneously over a period of 1.5 h. The mixture was stirred for 22 h at this temperature. The mixture was concentrated under reduced pressure to give a white residue, which was dissolved in EtOAc, washed with water and brine, and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane−EtOAc (2:1) to give **13** as a white amorphous solid (39.4 mg, 77% yield, dr = 82:18): $[\alpha]^{27}_D$ −17.7 [*c* 0.44 (dr = 82:18), $CHCl_3$]; IR (neat) 3311 (OH), 2253 (C≡C), 1415 (NSO_2), 1373 (NSO_2), 1173 (NSO_2), 1158 (NSO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.16 (dd, *J* = 6.7, 6.7 Hz, 1H), 2.36 (s, 3H), 2.43 (s, 3H), 2.46−2.52 (m, 1H), 2.76−2.82 (m, 1H), 2.95−3.03 (m, 1H), 3.41−3.52 (m, 2H), 3.78 (d, *J* = 3.9 Hz, 1H), 4.63 (dd, *J* = 6.8, 6.8 Hz, 1H), 4.72 (d, *J* = 3.9 Hz, 1H), 7.17 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.25 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 7.9 Hz, 1H), 7.66−7.70 (m, 3H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.99 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 21.6, 34.9, 42.9, 48.6, 53.1, 61.8, 78.7, 83.7, 112.9, 113.7, 117.2, 125.8, 126.2, 127.0 (4C), 127.5, 128.6, 129.8 (2C), 130.1 (2C), 134.6, 135.9, 136.8, 143.6, 145.8; HRMS (FAB) calcd $C_{29}H_{26}BrN_2O_6S_2$ $(M - H)^-$ 641.0421, found $(M - H)^-$ 641.0420.

***N*-[(*S*)-4-[(2*S*,3*R*)-3-(4-Bromo-1-tosyl-1*H*-indol-3-yl)oxiran-2-yl]-2-[(triisopropylsilyloxy)methyl]but-3-yn-1-yl]-4-methylbenzenesulfonamide (14).** To a stirred mixture of **13** (50 mg, 0.078 mmol) in CH_2Cl_2 (218 μL) were added 2,6-lutidine (25.7 μL, 0.234 mmol) and TIPSOTf (31.4 μL, 0.117 mmol) at 0 °C. The mixture was stirred for 3.5 h at this temperature and quenched by addition of saturated $NaHCO_3$. The whole was extracted with EtOAc. The extract was washed with saturated $NaHCO_3$ and brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane−EtOAc (4:1) to give **14** as a white amorphous solid (44.5 mg, 73% yield, dr = 82:18): $[\alpha]^{27}_D$ −32.6 [*c* 0.76 (dr = 82:18), $CHCl_3$]; IR (neat) 3286 (OH), 1416 (NSO_2), 1377 (NSO_2), 1175 (NSO_2), 1162 (NSO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92−1.02 (m, 21H), 2.35 (s, 3H), 2.41 (s, 3H), 2.43−2.48 (m, 1H), 2.86−2.92 (m, 1H), 2.99−3.04 (m, 1H), 3.35 (dd, *J* = 10.0, 10.0 Hz, 1H), 3.55 (dd, *J* = 10.0, 4.3 Hz, 1H), 3.76 (d, *J* = 3.9 Hz, 1H), 4.70 (d, *J* = 3.9 Hz, 1H), 4.94 (dd, *J* = 6.2, 6.2 Hz, 1H), 7.18 (dd, *J* = 8.4, 8.4 Hz, 1H), 7.25 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.62−7.68 (m, 3H), 7.76 (d, *J* = 8.4 Hz, 2H), 8.00 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.7 (3C), 17.8 (6C), 21.5, 21.6, 34.7, 44.9, 48.6, 53.2, 64.6, 78.3, 83.6, 112.9, 113.6, 117.3, 125.7, 126.3, 126.9 (2C), 127.0 (2C), 127.4, 128.6, 129.7 (2C), 130.1 (2C), 134.7, 136.0, 136.9, 143.3, 145.6; HRMS (FAB) calcd $C_{38}H_{46}BrN_2O_6S_2Si$ $(M - H)^-$ 797.1755, found $(M - H)^-$ 797.1757.

***N*-[(2*S*,5*R*)-6-(4-Bromo-1-tosyl-1*H*-indol-3-yl)-5-hydroxy-2-[(triisopropylsilyloxy)methyl]hex-3-yn-1-yl]-4-methylbenzenesulfonamide (17), *N*-[(2*S*,5*R*,*Z*)-6-(4-Bromo-1-tosylindolin-3-ylidene)-5-hydroxy-2-[(triisopropylsilyloxy)methyl]hex-3-yn-1-yl]-4-methylbenzenesulfonamide (18), and (*S*)-*N*-[6-(4-Bromo-1-tosyl-1*H*-indol-3-yl)-5-oxo-2-[(triisopropylsilyloxy)methyl]hex-3-yn-1-yl]-4-methylbenzenesulfonamide (19) (Table 2).** To a stirred mixture of $Zn(OTf)_2$ (27.3 mg, 0.075 mmol) and $NaBH_3CN$ (4.7 mg, 0.075 mmol) in THF (1.83 mL) was added **14** (20 mg, 0.025 mmol, dr = 82:18) at room temperature under argon. The mixture was allowed to warm to 60 °C and stirred for 2 h at this temperature, followed by quenching by addition of saturated $NaHCO_3$. The whole was extracted with EtOAc. The extract was washed with saturated $NaHCO_3$, water, and brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane−EtOAc (4:1) to give **17** (11 mg, 55% yield, dr = 82:18) and **19** (3.9 mg, 20% yield) (entry 8). When the reaction of **14** (20 mg, 0.025 mmol, dr = 82:18) was carried out with $ZnCl_2$ (1.00 M solution in Et_2O; 75 μL, 0.075 mmol) in place of $Zn(OTf)_2$, a isomeric mixture of **17** and **18** (11.8 mg, 59% yield, dr = 78:22) and **19** (1.5 mg, 7% yield) were obtained (entry 5). Compound **18** was isolated by HPLC [a Cosmosil 5C18-ARII column (20 × 250 mm, Nacalai Tesque, Inc., Kyoto, Japan), 254 nm, MeCN/H_2O = 90:10, 10 mL/min; for analytical HPLC: a Cosmosil 5C18-ARII column (4.6 × 250 mm, Nacalai Tesque, Inc., Kyoto, Japan), 254 nm, MeCN/H_2O = 90:10, 1 mL/min, *t* = 11.05 min].

Compound ***17***: white amorphous solid; $[\alpha]^{29}_D$ −23.3 [*c* 0.64 (single isomer), $CHCl_3$]; IR (neat) 3310 (OH), 1413 (NSO_2), 1375 (NSO_2), 1173 (NSO_2), 1159 (NSO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.00−1.08 (m, 21H), 1.91−2.00 (m, 1H), 2.35 (s, 3H), 2.41 (s, 3H), 2.69−2.75 (m, 1H), 3.11 (ddd, *J* = 12.0, 6.8, 5.7 Hz, 1H), 3.20 (ddd, *J* = 12.0, 5.7, 5.7 Hz, 1H), 3.30 (dd, *J* = 15.2, 6.9 Hz, 1H), 3.33 (dd, *J* = 15.2, 7.2 Hz, 1H), 3.58 (dd, *J* = 10.0, 8.6 Hz, 1H), 3.77 (dd, *J* = 10.0, 4.3 Hz, 1H), 4.65−4.70 (m, 1H), 5.15 (dd, *J* = 5.7, 5.7 Hz, 1H), 7.12 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.57 (s, 1H), 7.74 (d, *J* = 8.0 Hz, 2H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.96 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.8 (3C), 11.9 (6C), 21.5, 21.6, 34.6, 34.9, 45.1, 62.4, 64.8, 83.1, 84.4, 112.9, 114.3, 117.7, 125.4, 126.9 (3C), 127.1 (2C), 127.9, 128.6, 129.7 (2C), 130.0 (2C), 134.9, 136.4, 137.0, 143.4, 145.3; HRMS (FAB) calcd $C_{38}H_{48}BrN_2O_6S_2Si$ $(M - H)^-$ 799.1912, found $(M - H)^-$ 799.1910.

Compound ***18***: yellow amorphous solid; $[\alpha]^{27}_D$ −34.7 (*c* 0.44, $CHCl_3$); IR (neat) 3297 (OH), 1416 (NSO_2), 1362 (NSO_2), 1163 (NSO_2), 1093 (NSO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.99−1.08 (m, 21H), 1.57−1.72 (br m, 1H), 2.37 (s, 3H), 2.41 (s, 3H), 2.73−2.75 (m, 1H), 3.10−3.18 (m, 1H), 3.21−3.29 (m, 1H), 3.64 (dd, *J* = 9.9, 8.2 Hz, 1H), 3.80 (dd, *J* = 9.9, 4.4 Hz, 1H), 4.57−4.68 (m, 2H), 4.94 (d, *J* = 7.4 Hz, 1H), 5.32 (dd, *J* = 6.2, 6.2 Hz, 1H), 6.85−6.86 (m, 1H), 7.07 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.17 (d, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.67−7.71 (m, 3H), 7.75 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.8 (3C), 17.9 (6C), 21.5 (2C), 34.9, 44.9, 52.7, 59.9, 64.6, 82.7, 83.3, 113.3, 118.4, 122.7, 126.5, 127.1 (2C), 127.2 (2C), 128.9, 129.7 (2C), 130.0 (2C), 130.4, 133.6, 134.0, 136.9, 143.5, 144.8, 146.4; HRMS (FAB) calcd $C_{38}H_{48}BrN_2O_6S_2Si$ $(M - H)^-$ 799.1912, found $(M - H)^-$ 799.1910.

Compound ***19***: yellow amorphous solid; $[\alpha]^{27}_D$ −7.68 (*c* 0.44, $CHCl_3$); IR (neat) 2216 (C≡O), 1681 (C═O), 1415 (NSO_2), 1377 (NSO_2), 1162 (NSO_2), 1095 (NSO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.99−1.08 (m, 21H), 2.36 (s, 3H), 2.42 (s, 3H), 2.73−2.80 (m, 1H), 3.05 (ddd, *J* = 12.7, 6.4, 6.4 Hz, 1H), 3.17 (ddd, *J* = 12.7, 6.4, 6.3 Hz, 1H), 3.57 (dd, *J* = 9.9, 7.9 Hz, 1H), 3.72 (dd, *J* = 9.9, 4.4 Hz, 1H), 4.13 (s, 2H), 4.97 (dd, *J* = 6.4, 6.4 Hz, 1H), 7.13 (dd, *J* = 8.3, 8.3 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.3 Hz, 1H), 7.55 (s, 1H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.96 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.7 (3C), 17.9 (6C), 21.5, 21.6, 35.1, 42.3, 44.2, 63.8, 82.8, 91.7, 113.0, 114.3, 114.4, 125.7, 126.9 (2C), 127.1 (2C), 127.3, 127.8, 128.4, 129.8 (2C), 130.1 (2C), 134.8, 136.2, 136.8, 143.6, 145.5, 183.9; HRMS (FAB) calcd $C_{38}H_{46}BrN_2O_6S_2Si$ $(M - H)^-$ 797.1755, found $(M - H)^-$ 797.1754.

***N*-[(2*S*,4*R*)-6-(4-Bromo-1-tosyl-1*H*-indol-3-yl)-2-[(triisopropylsilyloxy)methyl]hexa-3,4-dienyl]-4-methylbenzenesulfonamide (3a).** To a stirred mixture of IPNBSH (39 mg, 0.150 mmol), PPh_3 (39 mg 0.150 mmol), and **17** (30 mg, 0.037 mmol, dr = 82:18) in THF (970 μL) was added diethyl azodicarboxylate (2.2 M solution in toluene; 68 μL, 0.150 mmol) at 0 °C under argon. The mixture was allowed to warm to room temperature and stirred for 2 h

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at this temperature. A mixture of TFE and water (1:1; 480 μL) was added to the reaction mixture to enable the formation of the propargylic diazene intermediate. After 16 h, the whole was extracted with Et_2O. The extract was washed with water and brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane−EtOAc (8:1) to give **3a** as a yellow amorphous solid (17 mg, 56% yield, dr = 82:18). Its purity was confirmed by ^{1}H NMR analysis. All of the spectral data were in agreement with those reported by us.[25]

***N*-[(2*S*,4*R*)-6-(4-Bromo-1-tosyl-1*H*-indol-3-yl)-2-(hydroxymethyl)hexa-3,4-dienyl]-4-methylbenzenesulfonamide (3b).** To a stirred solution of **3a** (59 mg, 0.075 mmol, dr = 82:18) in THF (6.8 mL) was added TBAF (1.00 M solution in THF; 150 μL, 0.150 mmol) at 0 °C. The mixture was stirred for 20 min at room temperature and quenched by addition of saturated NH_4Cl. The whole was extracted with EtOAc. The extract was washed with water and brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane−EtOAc (3:2) to give **3b** as a white amorphous (43.7 mg, 93% yield, dr = 82:18). Its purity was confirmed by ^{1}H NMR analysis. All the spectral data were in agreement with those reported by us.[7]

[(6a*R*,9*S*)-4,7-Ditosyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]-quinolin-9-yl]methanol (2a). To a stirred mixture of **3b** (20 mg, 0.032 mmol, dr = 82:18) in DMF (0.87 mL) were added $Pd(PPh_3)_4$ (3.7 mg, 0.0032 mmol) and K_2CO_3 (13.3 mg, 0.096 mmol) at room temperature under argon, and the mixture was stirred for 2.5 h at 100 °C. The mixture was quenched by addition of saturated NH_4Cl. The whole was extracted with EtOAc. The extract was washed with water and brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane−EtOAc (1:1) to give **2a** as a white amorphous solid (15.2 mg, 87% yield, dr = 87:13). Its purity was confirmed by ^{1}H NMR analysis. All of the spectral data were in agreement with those reported by us.[7]

■ ASSOCIATED CONTENT

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

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: hohno@pharm.kyoto-u.ac.jp; nfujii@pharm.kyoto-u.ac.jp.

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