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Enantioselective Total Synthesis of (+)-Lysergic Acid, (+)-Lysergol, and (+)-Isolysergol by Palladium-Catalyzed Domino Cyclization of Allenes Bearing Amino and Bromoindolyl Groups

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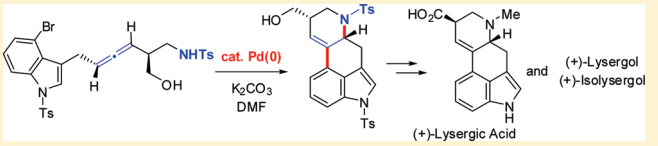
Supporting Information

ABSTRACT: Enantioselective total synthesis of the biologically important indole alkaloids (+)-lysergol, (+)-isolysergol, and (+)-lysergic acid is described. Key features of these total synthesis include (1) a facile synthesis of a chiral 1,3-amino alcohol via the Pd(0)- and In(I)-mediated reductive coupling reaction between L-serine-derived 2-ethynylaziridine and formaldehyde; (2) the Cr(II)/Ni(0)-mediated Nozaki−Hiyama−Kishi (NHK) reaction of an indole-3-acetaldehyde with iodoalkyne; and (3) Pd(0)-catalyzed domino cyclization of an allene bearing amino and bromoindolyl groups. This domino cyclization enabled direct construction of the C/D ring system of the ergot alkaloids skeleton, as well as the creation of the C5 stereogenic center with transfer of the allenic axial chirality to the central chirality.



Ergot alkaloids are pharmacologically important indole alkaloids, which are secondary metabolites produced by filamentous fungi such as *Claviceps purpurea* (Figure 1).[1] These alkaloids and several synthetic derivatives have been reported to exhibit broad biological activity.[2] For example, pergolide or bromocriptine are used as antiprolactin and anti-Parkinson's disease drugs. The characteristic structural feature of these alkaloids is a [*cd*]-fused indole, which contains the $\Delta^{9,10}$-double bond and chiral centers at C5 and C8 (Figure 1).

Because of their biological importance as well as structural appeal, ergot alkaloids, particularly lysergic acid (**1**), have attracted considerable interest from the synthetic community.[3] The pivotal steps toward the total synthesis are the construction of the C/D ring system controlling the stereochemistry at C5. Most synthetic studies have relied on a stepwise linear approach for the construction of the C/D ring system, except for Oppolzer's intramolecular imino-Diels−Alder strategy.[3d] Despite intensive synthetic investigations, there are only three asymmetric syntheses reported: Szántay in 2004[3j] and Fukuyama in 2009.[3k,l] The former involves optical resolution of the tetracyclic indole intermediate with (−)-dibenzoyl-L-tartaric acid, and the latter two utilize a stepwise or double cyclization strategy for the construction of the B/C ring. In contrast, total synthesis of (±)-lysergol and (±)-isolysergol has been reported by Ninomiya and Naito.[3m,n] More recently, Martin has completed an enantioselective synthesis of (+)-isolysergol, which is based on a late-stage diastereomeric ring-closing metathesis.[3o]

In recent years, palladium-catalyzed cyclizations of allenes bearing a nucleophilic functionality represent an attractive approach for the construction of heterocycles.[4] The combination of aryl halides, allenes, and nucleophiles such as amines or alcohols

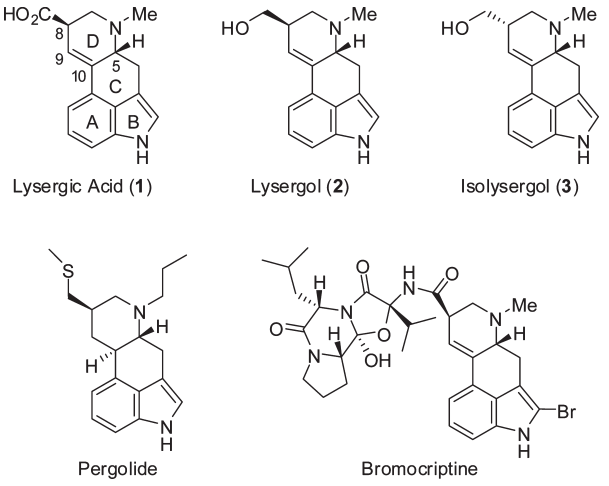


Figure 1. Indole alkaloids of the ergot family and synthetic derivatives.

in the palladium(0)-catalyzed reaction enables the direct formation of carbon−carbon and carbon−heteroatom bonds.[5−7] Therefore, several efficient domino cyclizations of allenes bearing an amino group have been developed; however, the reaction of allenes having an aryl halide and amino group at both ends of internal allenes is unprecedented. We expected palladium-catalyzed domino cyclization of allene **5a** (Scheme 1) to provide

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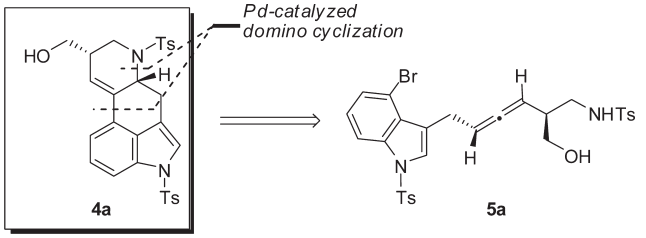
Scheme 1. Our Plan for the Direct Construction of the Ergot Alkaloid Core Structure



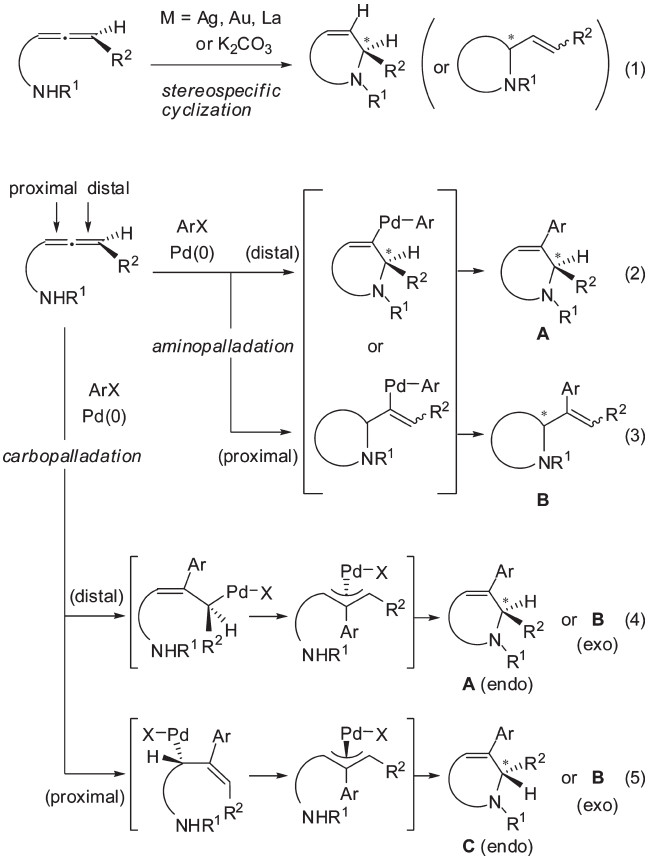
direct access to the core structure **4a** of ergot alkaloids, including lysergic acid (**1**), lysergol (**2**), and isolysergol (**3**). It is well-known that the axial chirality of allenes is stereospecifically transferred into the new stereogenic centers in the cases of Ag-,[8] Au-,[9] organolanthanide-,[10] or K_2CO_3-mediated[11] cyclization of allenes bearing an amino group (Scheme 2, eq 1). In contrast, when using palladium-catalyzed cyclization with aryl halides, prediction of the product distribution including stereo- and regioisomers is more difficult, because these types of reactions may proceed through two competing pathways (Scheme 2): the aminopalladation pathway,[6,12] where the arylpalladium halide would activate the distal double bond from the less hindered side (eq 2), affords the *endo*-type cyclization product **A** stereospecifically through reductive elimination, while the reaction at the proximal double bond gives its regioisomer **B** (eq 3). On the other hand, carbopalladation[5,13] onto the distal double bond from the less hindered side (eq 4) followed by *anti*-cyclization of the η^3-allylpalladium intermediate by the nitrogen nucleophile would give the *endo*-cyclization product **A**, which has the same configuration as the product formed by distal bond aminopalladation (eq 2). However, the reaction at the proximal double bond would provide the *endo*-cyclization product **C** (eq 5), which has the opposite configuration to the distal aminopalladation product **A** (eq 2). Consideration of the *exo*-type cyclization to produce **B** from the η^3-allylpalladium intermediate will make the prediction more complicated.[5b−e,h,i,o]

We describe herein our investigation on the direct construction of the ergot alkaloids skeleton using a palladium-catalyzed domino cyclization of chiral allene **5a** bearing a protected 4-bromoindol-3-yl group and a free hydroxy group. This bis-cyclization would allow the simultaneous construction of the C/D ring system and the creation of the C5 chiral center. The challenges in this domino cyclization are (1) sequential regioselective formation of a carbon−carbon bond and a carbon−nitrogen bond for the construction of the desired 6,6-fused C/D ring system and (2) transfer of an axial chirality in the starting allene to the central chirality at C5.[14] Enantioselective total synthesis of lysergic acid (**1**), lysergol (**2**), and isolysergol (**3**) based on this strategy is also presented.

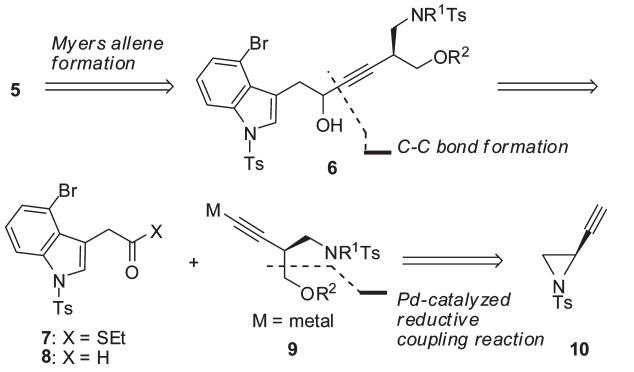
RESULTS AND DISCUSSION

Synthesis of Allenic Amide 5. Retrosynthetic analysis of the allenes **5** is shown in Scheme 3. We planned to synthesize both diastereomeric allenes **5** in order to examine the difference in reactivity between these isomers. The chiral allene unit of **5** would form from chiral propargyl alcohol **6** using the Myers method.[15] The propargyl alcohol **6** could be obtained by C−C

Scheme 2. Product Distribution of Transition-Metal-Mediated Cyclization of Allenes Bearing an Amino Group



Scheme 3. Retrosynthetic Analysis of Allenes 5



bond formation reaction of thioester **7** or aldehyde **8** with metal acetylide **9**, in combination with asymmetric hydrogenation if necessary. The precursor of the acetylide **9** can be accessed from L-serine-derived chiral 2-ethynylaziridine **10** by a reductive coupling reaction with formaldehyde in the presence of Pd-$(PPh_3)_4$ and InI, as we previously reported.[16]

Initially, we investigated the palladium-catalyzed reductive coupling reaction of ethynylaziridine **10** (Table 1). The aziridine **10** was easily prepared in an enantioenriched form (97% ee) by a four-step sequence from the (*S*)-Garner's aldehyde[17] (alkyne

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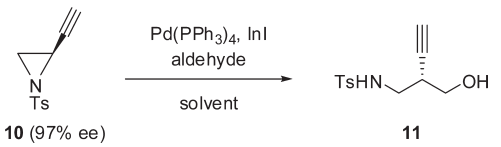
Table 1. Reductive Coupling Reaction of 2-Ethynylaziridine 10 with Formaldehyde[a]



10 (97% ee) **11**

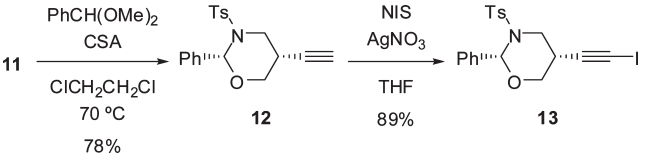
entry	aldehyde	solvent	additive (equiv)	yield (%)[b]	ee (%)[c]
1	$(CH_2O)_n$	THF/HMPA (4:1)	H_2O (1.0)	78	96
2	$(CH_2O)_n$	THF/DMPU (4:1)	H_2O (1.0)	77	83
3	$(CH_2O)_n$	THF/H_2O (1:1)		50	92
4	$(CH_2O)_n$	DMF/H_2O (1:1)		15	58
5	$(CH_2O)_n$	THF		ca. 42	91
6	formalin	THF/HMPA (4:1)		83	97
7[d]	formalin	THF/HMPA (4:1)		88 (70[e])	97 (99[e])

[a] Reactions were carried out using the aziridine **10** (97% ee) with $Pd(PPh_3)_4$ (5 mol %), InI (1.3 equiv) and aldehyde (2.0 equiv) for 1.5−4 h. [b] Isolated yields. [c] Determined by chiral HPLC (OD-H) analysis. [d] Reaction was carried out with $Pd(PPh_3)_4$ (3 mol %) and InI (1.2 equiv) on a 4 g scale. [e] After single recrystallization.

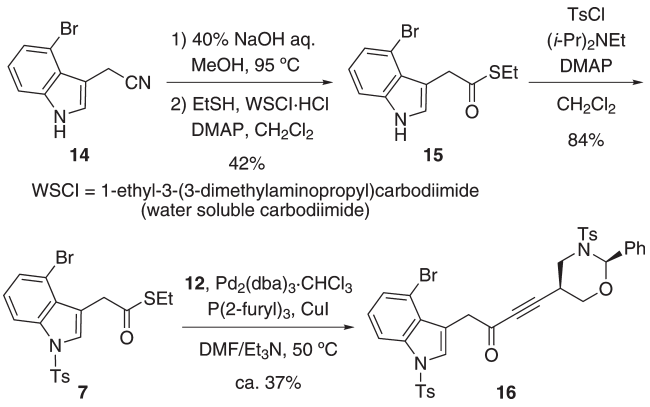
formation, deprotection, *N*-tosylation, and aziridine formation), following our reported procedure.[18] Our previous study revealed that the reductive coupling reaction of 2,3-*cis*- or 2,3-*trans*-2-ethynylaziridines efficiently reacts with alkyl or aryl aldehyde in the presence of InI and a catalytic amount of Pd(0) to produce 2-ethynyl-1,3-amino alcohols in a highly stereoselective manner (mostly >99:1).[16] In the present case, using the aziridine **10** lacking the 3-substituent required careful investigation, because the stereoselectivity of the reaction would be reflected in the enantiomeric purity of the resulting amino alcohol **11**. Treatment of **10** with $(CH_2O)_n$, $Pd(PPh_3)_4$ (5 mol %), and InI in THF/HMPA (standard conditions for the preparation and addition of the allenylindium reagents)[16] produced the desired 1,3-amino alcohol **11** (96% ee) in 78% yield (entry 1). Changing the reaction solvent from THF/HMPA to THF/DMPU, THF/H_2O, DMF/H_2O, or THF only decreased the optical purity of the desired product **11** without improving the yield (entries 2−5). Use of formalin instead of $(CH_2O)_n$ afforded the desired product in a higher yield (83%) in good stereoselectivity (97% ee, entry 6). Conducting the reaction on a 4 g scale also gave the desired product in satisfactory yield (88%, entry 7), and the enantiomerically pure alcohol **11** was obtained after single recrystallization. Protection of the 1,3-amino alcohol **11** as benzylidene acetal provided the desired alkyne **12**,[19] which was allowed to react with NIS and $AgNO_3$ to give the corresponding iodoalkyne **13** (Scheme 4).[20]

We next examined the preparation of ynone **16** by palladium-mediated coupling of a thioester with an alkyne, which is known to proceed under mild conditions (Scheme 5).[21] The requisite thioester **7** for the coupling reaction was prepared by the hydrolysis of a known nitrile **14**,[22] thioesterification, and *N*-protection of indole. Unfortunately, the reaction of **7** with the alkyne **12** in the presence of $Pd_2(dba)_3 \cdot CHCl_3$ (5 mol %), P(2-furyl)$_3$, and CuI in DMF/Et_3N at 50 °C afforded the desired product **16** in low yield (ca. 37%) along with several unidentified side products.

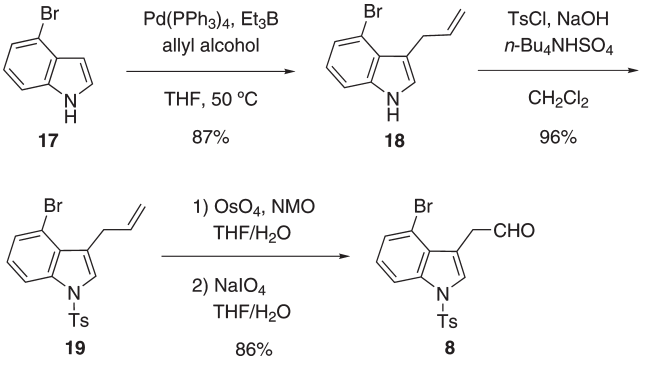
Scheme 4. Synthesis of Iodoalkyne 13



Scheme 5. Synthesis of Ynone 16 by Palladium-Catalyzed Coupling of Thioester 15 with Alkyne 12



Scheme 6. Synthesis of Aldehyde 8



We next investigated the cross-coupling reaction of the alkyne **12** or iodoalkyne **13** with (4-bromoindol-3-yl)acetaldehyde **8** (Table 2), which was prepared from commercially available 4-bromoindole **17** as follows (Scheme 6). 3-Allylindole **18** was obtained using palladium-catalyzed C3-selective allylation of indoles with allyl alcohol and triethylborane, reported by Tamaru.[23] *N*-Protection of indole **18**[24] followed by OsO_4/$NaIO_4$-mediated oxidative cleavage of the double bond gave the desired aldehyde **8**. The addition of **12**-derived lithium acetylide with the aldehyde **8** provided the desired propargyl alcohol **20** in a moderate yield (50%, dr = 1:1, Table 2, entry 1). Addition of $CeCl_3$ improved the yield to 67% (entry 2).[25] In contrast, mild conditions using $InBr_3$[26] or Et_2Zn[27] did not afford the desired product, although the starting aldehyde was consumed (entries 3 and 4). Successful cross-coupling was achieved using the Cr(II)/Ni(0)-mediated Nozaki−Hiyama−Kishi (NHK)

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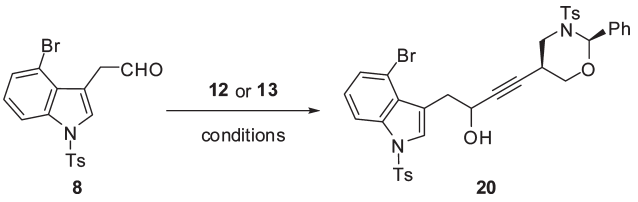
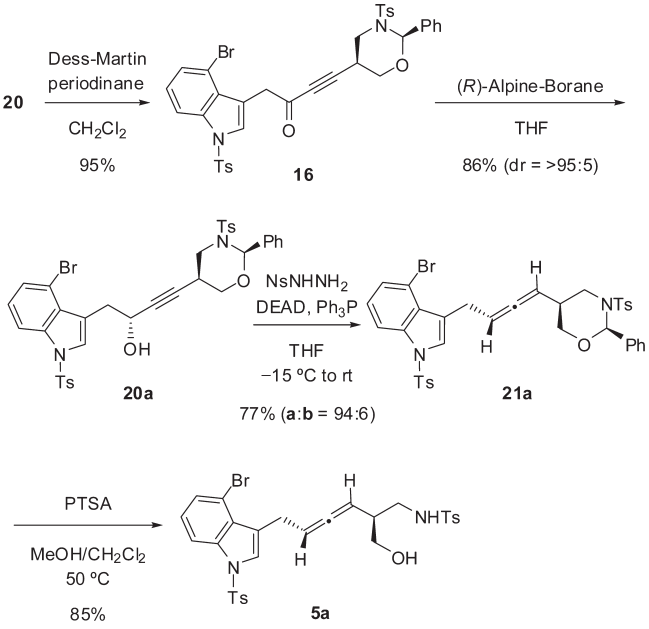
Table 2. C−C Bond Formation Reaction of Aldehyde 8 with Alkyne 12 or Iodoalkyne 13



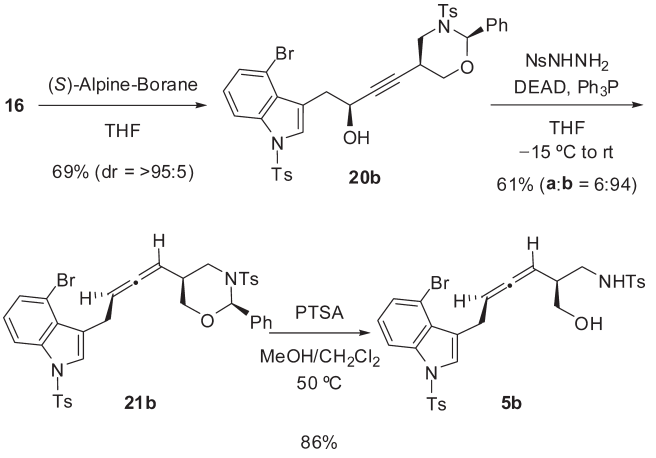
entry	substrate	conditions	yield (%)[a]	dr[b]
1	**12**	*n*-BuLi, THF, −78 °C	50	1:1
2	**12**	*n*-BuLi, $CeCl_3$, THF, −78 °C	67	1:1
3	**12**	$InBr_3$, (*R*)-BINOL, Cy_2NMe, CH_2Cl_2, 40 °C	ND	
4	**12**	Et_2Zn, (*S*)-BINOL, $Ti(Oi\text{-}Pr)_4$, toluene/THF, 0 °C	ND	
5	**13**	$NiCl_2$, $CrCl_2$, THF, 0 °C	90	1:1

[a] Isolated yields. [b] Determined by ^1H NMR analysis.

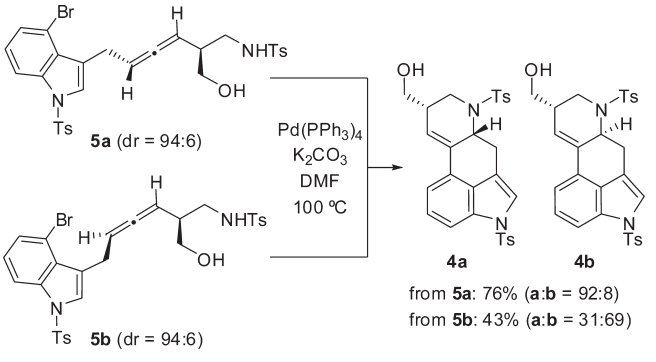
Scheme 7. Synthesis of Allenic Amide 5a



Scheme 8. Synthesis of Allenic Amide 5b



Scheme 9. Palladium-Catalyzed Domino Cyclization of Allenic Amides 5a and 5b



reaction with **8** and the iodoalkyne **13**, leading to the desired product **20** in 90% yield (dr = 1:1, entry 5).[28,29]

With the propargyl alcohol **20** in hand, we attempted the conversion to each isomer of the requisite allenic amides **5** for the palladium-catalyzed domino cyclization (Scheme 7 and 8). Dess−Martin oxidation of **20** followed by reduction with (*R*)-Alpine-Borane[30,31] furnished the desired propargyl alcohol **20a** in 86% yield with high diastereoselectivity (dr = >95:5, Scheme 7). This alcohol was stereoselectively transformed into the allene **21a** by the Myers method using nosyl hydrazine under Mitsunobu conditions.[15] Subsequent cleavage of the benzylidene group of **21a** with PTSA gave the allenic amide **5a** (dr = 94:6).[32] The diastereomeric allenic amide **5b** (dr = 94:6) was similarly prepared from the same propargyl ketone **16**, via reduction with (*S*)-Alpine-Borane (Scheme 8).

Palladium-Catalyzed Domino Cyclization of Allenic Amides 5. We next examined the construction of the ergot alkaloid skeleton via the palladium-catalyzed domino cyclization

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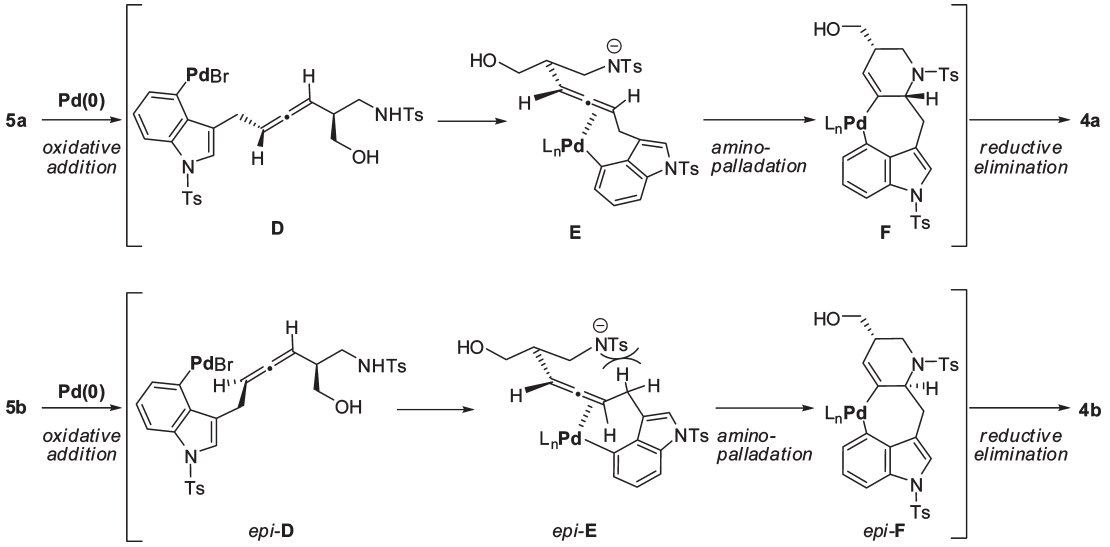
Scheme 10. Proposed Mechanism for Domino Cyclization

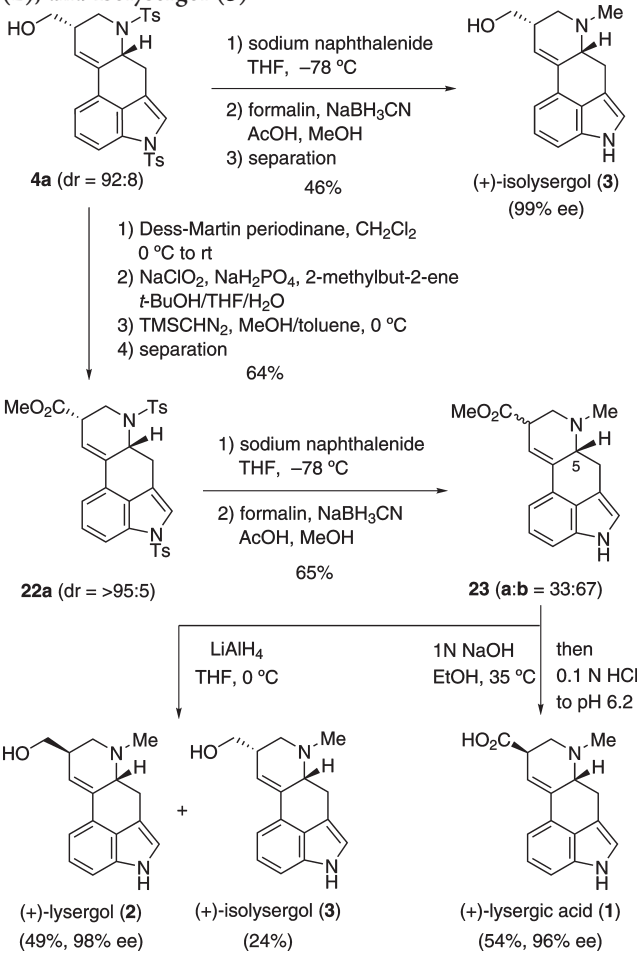


of the allenic amides **5** bearing a free hydroxy group (Scheme 9). The reaction was conducted using a 94:6 diastereomixture of **5a** and **5b** because of the difficulty in separating each of the diastereomers. Reaction of **5a** with 5 mol % of $Pd(PPh_3)_4$ and K_2CO_3 in DMF at 100 °C (the optimized conditions for the domino cyclization of racemic model substrates[14]) provided the desired product **4** in 76% yield with good diastereoselectivity (**a**:**b** = 92:8).[33] The dihydropyran derivatives[5n,t] (the cyclization by the hydroxy group) and/or the azetidine derivatives[5c,f,i] (the proximal cyclization by the NHTs group) were not isolated as side products. When the diastereomeric allenic amide **5b** was subjected to the same conditions, the yield and stereoselectivity of the reaction were dramatically reduced (43% yield, **a**:**b** = 31:69). These results show a clear difference in reactivity between the diastereomeric substrates.

As already mentioned, this type of domino cyclization could proceed through two pathways: aminopalladation or carbopalladation (Scheme 2). In the present case, the aminopalladation pathway can explain the results obtained with **5a** and **5b**: aminopalladation of indolylpalladium halide **D** (Scheme 10), formed by oxidative addition of **5a** to Pd(0), would proceed through conformation **E** to produce alkenylpalladium(II) intermediate **F** stereoselectively. This is followed by reductive elimination leading to **4a** as the major isomer. Similarly, cyclization of **5b**-derived intermediate *epi*-**D** produces **4b** through *epi*-**E**; however, unfavorable steric interaction between the tosylamide group and the methylene protons both located on the same side destabilizes this conformer, which would decrease reactivity of **5b** toward aminopalladation via *epi*-**E**.[34] Thus, the cyclization reaction of the allenic amide **5b** may partially involve aminopalladation through other conformers or the competing carbopalladation pathway.

Total Synthesis of Lysergic Acid (1), Lysergol (2), and Isolysergol (3). With the ergot derivatives **4** with all the requisite functionalities in hand, we then focused on the total synthesis of isolysergol (**3**), lysergol (**2**) and lysergic acid (**1**) (Scheme 11). Cleavage of the tosyl groups of **4a** with sodium naphthalenide and subsequent *N*-methylation led to (+)-isolysergol (**3**) in 46% yield (99% ee, Chiralcel OD-H).[3o] Oxidation

Scheme 11. Total Synthesis of Lysergic Acid (1), Lysergol (2), and Isolysergol (3)



of the primary alcohol of **4a** with the Dess–Martin reagent[35] and $NaClO_2$ followed by esterification with $TMSCHN_2$ gave the

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corresponding methyl ester **22a** (64%, 3 steps), after separation of the diastereomers.[36] Cleavage of two tosyl groups with sodium naphthalenide and subsequent *N*-methylation led to a diastereomixture of methyl isolysergate **23a** and lysergate **23b** (65%, **a**:**b** = 33:67). By reduction of **23** (**a**:**b** = 33:67) with $LiAlH_4$, (+)-lysergol (**2**) was obtained in 49% yield (98% ee, Chiralcel OD-H), along with (+)-isolysergol (**3**) (24%).[37] Finally, hydrolysis of **23** (**a**:**b** = 33:67) with NaOH accompanying isomerization to the natural isomer[3i,j] furnished (+)-lysergic acid (**1**) in 54% yield (96% ee, Chiralcel OD-H after methylation with TMSCHN_2).[38,39] All of the spectroscopic data were in agreement with those of natural and synthetic lysergic acid, lysergol, and isolysergol reported in the literature.[3i,j,o,14]

CONCLUSIONS

In conclusion, the enantioselective total synthesis of (+)-lysergol, (+)-isolysergol, and (+)-lysergic acid has been accomplished. (+)-Lysergic acid was prepared in 15 steps from the known ethynylaziridine (4.0% overall yield; 19 steps, 1.1% overall yield from the Garner's aldehyde). Our synthesis highlights a strategy for constructing the C/D ring system of the core structure of ergot alkaloids based on palladium-catalyzed domino cyclization of allene, which allows the creation of the stereochemistry at C5 by transfer of the axial chirality of allene to the central chirality. Other key features of the syntheses include the Pd(0)/In(I)-mediated reductive coupling reaction of chiral 2-ethynylaziridine with formaldehyde and the Cr(II)/Ni(0)-mediated NHK reaction of indole-3-acetaldehyde with iodoalkyne.

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).

(*S*)-*N*-[2-(Hydroxymethyl)but-3-ynyl]-4-methylbenzenesulfonamide (11) (Table 1, Entry 7). To a stirred mixture of aziridine **10** (4.00 g, 18.1 mmol, 97% ee) in THF/HMPA (150 mL, 4:1) were added $Pd(PPh_3)_4$ (627 mg, 0.54 mmol), InI (5.25 g, 21.7 mmol), and formalin (2.7 mL, 36.2 mmol) at room temperature under argon. The mixture was stirred for 2.5 h at this temperature and filtered through a short pad of silica gel with EtOAc to give a crude **11**. The residue was dissolved in Et_2O, washed with H_2O and brine, and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give a yellow oil, which was purified by flash chromatography over silica gel with *n*-hexane−EtOAc (2:1) to give **11** as a yellow solid {4.01 g, 88% yield, 97% ee [HPLC, Chiralcel-OD column eluting with 90:10 *n*-hexane/EtOH at 0.5 mL/min, t_1 = 26.10 min (major isomer), t_2 = 30.67 min (minor isomer)]}. Recrystallization from *n*-hexane−EtOAc gave pure **11** (3.23 g, 99% ee) as colorless crystals: mp 86−87 °C; $[\alpha]^{26}_D$ −14.8 (*c* 1.06, $CHCl_3$); IR (neat) 3289 (OH), 1327 (NSO_2), 1158 (NSO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.15 (d, *J* = 2.3 Hz, 1H), 2.39 (t, *J* = 6.6 Hz, 1H), 2.43 (s, 3H), 2.69−2.77 (m, 1H), 3.14 (ddd, *J* = 12.6, 6.6, 5.7 Hz, 1H), 3.21 (ddd, *J* = 12.6, 6.6, 5.1 Hz, 1H), 3.72−3.77 (m, 2H), 5.07 (t, *J* = 6.6 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.75 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 34.7, 43.2, 62.2, 72.7, 81.3, 127.0 (2C), 129.8 (2C), 136.8, 143.7. Anal. Calcd for $C_{12}H_{15}NO_3S$: C, 56.90; H, 5.97; N, 5.53. Found: C, 56.74; H, 5.84; N, 5.50.

(2*R*,5*S*)-5-Ethynyl-2-phenyl-3-tosyl-1,3-oxazinane (12). To a stirred mixture of **11** (1.70 g, 6.70 mmol) and $PhCH(OMe)_2$ (2.0 mL, 13.4 mmol) in $ClCH_2CH_2Cl$ (40 mL) was added camphor-10-sulfonic acid (156 mg, 0.67 mmol) at room temperature. The mixture was stirred for 14 h at 70 °C and quenched with saturated $NaHCO_3$. The mixture was diluted with EtOAc. The organic phase was separated, washed with H_2O 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 (10:1) to give **12** as a white solid (1.78 g, 78% yield). Recrystallization from *n*-hexane−EtOAc gave pure **12** as colorless crystals: mp 125−126 °C; $[\alpha]^{27}_D$ −57.3 (*c* 0.93, $CHCl_3$); IR (neat) 1348 (NSO_2), 1167 (NSO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.96 (d, *J* = 2.3 Hz, 1H), 2.25−2.35 (m, 1H), 2.47 (s, 3H), 3.18 (dd, *J* = 14.9, 12.0 Hz, 1H), 3.55 (dd, *J* = 11.6, 11.2 Hz, 1H), 3.70 (dd, *J* = 11.6, 4.6 Hz, 1H), 4.01 (dd, *J* = 14.9, 4.6 Hz, 1H), 6.70 (s, 1H), 7.34−7.38 (m, 1H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.41−7.48 (m, 4H), 7.87 (d, *J* = 8.0 Hz, 2H); ^{1}H NMR (500 MHz, C_6D_6) δ 1.45 (d, *J* = 2.9 Hz, 1H), 1.83 (s, 3H), 2.32−2.39 (m, 1H), 3.19 (dd, *J* = 14.9, 11.7 Hz, 1H), 3.44 (dd, *J* = 11.3, 5.0 Hz, 1H), 3.48 (dd, *J* = 11.3, 10.8 Hz, 1H), 4.22 (dd, *J* = 14.9, 4.6 Hz, 1H), 6.72 (d, *J* = 8.0 Hz, 2H), 6.92 (s, 1H), 7.04 (t, *J* = 7.4 Hz, 1H), 7.10 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.44 (d, *J* = 7.4 Hz, 2H), 7.75 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 25.5, 43.9, 63.2, 72.0, 79.8, 83.0, 127.0 (2C), 127.5 (2C), 128.5, 129.1 (2C), 130.0 (2C), 135.0, 137.5, 144.0. Anal. Calcd for $C_{19}H_{19}NO_3S$: C, 66.84; H, 5.61; N, 4.10. Found: C, 66.91; H, 5.71; N, 4.04.

(2*R*,5*S*)-5-(Iodoethynyl)-2-phenyl-3-tosyl-1,3-oxazinane (13). To a stirred mixture of **12** (100 mg, 0.29 mmol) in THF (1.0 mL) were added *N*-iodosuccinimide (98.8 mg, 0.44 mmol) and $AgNO_3$ (7.39 mg, 0.044 mmol) at room temperature. The mixture was stirred for 2 h at this temperature and quenched with ice-cold H_2O. The whole was extracted with EtOAc. The extract was washed with saturated $Na_2S_2O_3$, H_2O, and brine, dried over $MgSO_4$, and concentrated under pressure to give a white solid, which was purified by column chromatography over silica gel with *n*-hexane−EtOAc (10:1) to give **13** (121 mg, 89% yield). Recrystallization from benzene gave pure **13** as colorless crystals: mp 75−76 °C; $[\alpha]^{27}_D$ −108.9 (*c* 1.00, $CHCl_3$); IR (neat) 1343 (NSO_2), 1165 (NSO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.39−2.47 (m, 1H), 2.47 (s, 3H), 3.17 (dd, *J* = 14.9, 12.0 Hz, 1H), 3.54 (dd, *J* = 11.5, 10.9 Hz, 1H), 3.65−3.72 (m, 1H), 3.99 (dd, *J* = 14.9, 4.6 Hz, 1H), 6.68 (s, 1H), 7.34−7.37 (m, 1H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.41−7.47 (m, 4H), 7.86 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −0.7, 21.6, 27.7, 44.0, 63.2, 83.0, 90.0, 127.1 (2C), 127.5 (2C), 128.6, 129.2 (2C), 130.1 (2C), 134.9, 137.4, 144.1. Anal. Calcd for $C_{19}H_{18}NO_3S\cdot 0.75C_6H_6$: C, 53.67; H, 4.31; N, 2.66. Found: C, 53.77; H, 4.31; N, 2.57.

***S*-Ethyl 2-(4-Bromo-1*H*-indol-3-yl)ethanethioate (15).** The hydrolysis of 4-bromo-3-indoleacetonitrile **14** was carried out according to the method of Somei.[22] To a stirred solution of the 4-bromo-3-indoleacetonitrile **14** (6.28 g, 26.8 mmol) in MeOH (200 mL) was added 40% aq NaOH (200 mL), and the mixture was stirred for 4.5 h at 95 °C. MeOH was removed under reduced pressure. After addition of brine, the whole was made acidic by adding conc HCl and then extracted with CH_2Cl_2. The extract was washed with brine and dried over $MgSO_4$. Concentration of the filtrate under reduced pressure gave 3.5 g of crude indoleacetic acid, which was used without further purification. To a stirred solution of the indoleacetic acid in CH_2Cl_2 (160 mL) were added DMAP (84.3 mg, 0.69 mmol), EtSH (3.23 mL, 55.3 mmol), and WSCI·HCl (3.21 g, 16.7 mmol) at 0 °C. After stirring for 2.5 h at room temperature, H_2O was added, and the mixture was concentrated under reduced pressure. The residue was diluted with EtOAc. The extract was washed with H_2O and brine, dried over $MgSO_4$, and concentrated under pressure to give a white solid, which was purified by column chromatography over silica gel with *n*-hexane−EtOAc (5:1) to give **15** (3.38 g, 42% yield). Recrystallization

from *n*-hexane−EtOAc gave pure **15** as colorless crystals: mp 96−97 °C; IR (neat) 3378 (NH), 1658 (C═O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, J = 7.4 Hz, 3H), 2.87 (q, J = 7.4 Hz, 2H), 4.22 (s, 2H), 7.00 (dd, J = 7.8, 7.8 Hz, 1H), 7.11 (d, J = 2.4 Hz, 1H), 7.27 (d, J = 7.8 Hz, 1H), 7.27 (d, J = 7.8 Hz, 1H), 8.31 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6, 23.5, 41.1, 108.9, 110.7, 114.2, 123.2, 124.3, 125.5, 126.1, 137.4, 199.8. Anal. Calcd for $C_{12}H_{12}BrNOS$: C, 48.33; H, 4.06; N, 4.70. Found: C, 48.46; H, 4.09; N, 4.69.

S-Ethyl 2-(4-Bromo-1-tosyl-1*H*-indol-3-yl)ethanethioate (7). To a stirred solution of thioester **15** (3.38 g, 11.4 mmol) in CH_2Cl_2 (50 mL) were added TsCl (4.77 g, 25.0 mmol), $(i\text{-Pr})_2$NEt (4.36 mL, 25.0 mmol), and DMAP (278 mg, 2.28 mmol) at 0 °C. The mixture was stirred for 5 h at this temperature and quenched with saturated NH_4Cl. The whole was extracted with EtOAc. The extract was washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated under pressure to give a white solid, which was purified by column chromatography over silica gel with *n*-hexane−EtOAc (10:1) to give **7** (4.35 g, 84% yield). Recrystallization from *n*-hexane−EtOAc gave pure **7** as colorless crystals: mp 99−100 °C; IR (neat) 1680 (C═O), 1372 (NSO_2), 1173 (NSO_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, J = 7.4 Hz, 3H), 2.35 (s, 3H), 2.87 (q, J = 7.4 Hz, 2H), 4.15 (s, 2H), 7.13 (dd, J = 8.0, 8.0 Hz, 1H), 7.24 (d, J = 8.3 Hz, 2H), 7.38 (d, J = 8.0 Hz, 1H), 7.60 (s, 1H), 7.75 (d, J = 8.3 Hz, 2H), 7.95 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6, 21.6, 23.6, 40.9, 112.9, 114.5, 115.0, 125.7, 126.9 (2C), 127.8, 127.9, 128.6, 130.0 (2C), 134.8, 136.3, 145.3, 197.5. Anal. Calcd for $C_{19}H_{18}BrNO_3S_2$: C, 50.44; H, 4.01; N, 3.10. Found: C, 50.21; H, 4.01; N, 3.02.

3-Allyl-4-bromo-1*H*-indole (18). The allylation of 4-bromoindole **17** was carried out according to the method of Tamaru.[23] To a stirred mixture of 4-bromoindole **17** (5.00 g, 25.5 mmol) in THF (65 mL) were added $Pd(PPh_3)_4$ (884 mg, 0.765 mmol), Et_3B (1.02 M solution in hexane; 7.5 mL, 7.65 mmol) and allyl alcohol (1.75 mL, 25.8 mmol) at room temperature under argon, and the mixture was stirred for 17 h at 50 °C. The mixture was concentrated under reduced pressure to give a brown oil, which was purified by flash chromatography over silica gel with *n*-hexane−EtOAc (8:1) to give **18** as a brown oil (5.24 g, 87% yield). Its purity was confirmed by ^{1}H NMR analysis. All spectral data were in agreement with those reported by Tamaru.[23]

3-Allyl-4-bromo-1-tosyl-1*H*-indole (19). To a stirred solution of allylbromoindole **18** (5.24 g, 22.2 mmol), NaOH (2.66 g, 66.6 mmol), and *n*-Bu_4NHSO_4 (754 mg, 2.22 mmol) in CH_2Cl_2 (190 mL) was added TsCl (4.65 g, 24.4 mmol) at 0 °C. After stirring for 2.5 h at room temperature, 1,3-diaminopropane (1.11 mL, 13.3 mmol) and Et_3N (1.84 mL, 13.3 mmol) were added. The mixture was stirred for 2 h at this temperature, and H_2O was added. The whole was extracted with EtOAc. The extract was washed with 1 N HCl, H_2O, and brine and dried over $MgSO_4$. Concentration under pressure gave a white solid, which was purified by column chromatography over silica gel with *n*-hexane−EtOAc (10:1) to give **19** (8.36 g, 96% yield). Recrystallization from *n*-hexane−EtOAc gave pure **19** as colorless crystals. Its purity was confirmed by ^{1}H NMR and elemental analyses. All spectral data were in agreement with those reported by Hegedus.[24]

2-(4-Bromo-1-tosyl-1*H*-indol-3-yl)acetaldehyde (8). To a stirred mixture of **19** (700 mg, 1.79 mmol) and NMO (377 mg, 3.22 mmol) in THF/H_2O (14 mL, 3:1) was added OsO_4 (2.5 wt % *t*-BuOH, 0.912 mL, 0.090 mmol) at 0 °C. The mixture was stirred for 14 h at room temperature and quenched with saturated Na_2SO_3. After stirring for 15 min, the whole was extracted with EtOAc. The extract was washed with H_2O and brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give a crude diol as a white amorphous solid, which was used without further purification. To a stirred solution of this diol in THF/H_2O (14 mL, 3:1) was added $NaIO_4$ (1.53 g, 7.16 mmol) at room temperature. After stirring for 2.5 h at this temperature, the mixture was diluted with EtOAc. The organic phase was separated, washed with H_2O 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 **8** as a yellow oil (606 mg, 86% yield): IR (neat) 1725 (C═O), 1371 (NSO_2), 1172 (NSO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.35 (s, 3H), 4.06 (s, 2H), 7.15 (dd, J = 8.6, 8.6 Hz, 1H), 7.24 (d, J = 8.0 Hz, 2H), 7.37 (d, J = 8.6 Hz, 1H), 7.58 (s, 1H), 7.76 (d, J = 8.0 Hz, 2H), 7.97 (d, J = 8.6 Hz, 1H), 9.87 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 40.8, 113.0, 113.8, 114.2, 125.8, 126.9 (3C), 127.8, 128.3, 130.0 (2C), 134.8, 136.2, 145.5, 198.6. HRMS (FAB) calcd $C_{17}H_{15}BrNO_3S$: $(M + H)^+$ 391.9956, found $(M + H)^+$ 391.9954.

(*R*)-1-(4-Bromo-1-tosyl-1*H*-indol-3-yl)-4-[(2*R*,5*S*)-2-phenyl-3-tosyl-1,3-oxazinan-5-yl]but-3-yn-2-ol (20a) and Its (*S*)-Isomer (20b) (Table 2, Entry 5). To a stirred mixture of $NiCl_2$ (3.25 mg, 0.025 mmol) and $CrCl_2$ (324 mg, 2.51 mmol) in THF (6.3 mL) was added a solution of aldehyde **8** (246 mg, 0.63 mmol) and alkyne **13** (645 mg, 1.38 mmol) in THF (6.3 mL) at 0 °C under argon. The mixture was stirred for 4.5 h at this temperature. The mixture was diluted with Et_2O and quenched with H_2O. The whole was extracted with EtOAc. The organic phase was separated, washed with saturated $Na_2S_2O_3$ 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 (3:1) to give **20** as a pale yellow amorphous solid (414 mg, 90% yield, dr = 1:1).

1-(4-Bromo-1-tosyl-1*H*-indol-3-yl)-4-[(2*R*,5*S*)-2-phenyl-3-tosyl-1,3-oxazinan-5-yl]but-3-yn-2-one (16). To a stirred solution of alcohol **20** (2.64 g, 3.60 mmol) in CH_2Cl_2 (118 mL) was added Dess−Martin periodinane (3.37 g, 7.92 mmol) at 0 °C. After stirring for 20 min at this temperature, the mixture was allowed to warm to room temperature. The mixture was stirred for further 40 min at this temperature and quenched with saturated $Na_2S_2O_3$ and saturated $NaHCO_3$. The whole was extracted with EtOAc. The extract was washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated under pressure to give an oily residue, which was purified by column chromatography over silica gel with *n*-hexane−EtOAc (3:1) to give **16** as a yellow amorphous solid (2.49 g, 95% yield): $[\alpha]^{28}_D$ −61.0 (*c* 1.17, $CHCl_3$); IR (neat) 2215 (C≡C), 1677 (C═O), 1375 (NSO_2), 1350 (NSO_2), 1171 (NSO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.31−2.38 (m, 1H), 2.35 (s, 3H), 2.48 (s, 3H), 3.00 (dd, J = 14.6, 11.7 Hz, 1H), 3.35 (dd, J = 11.5, 10.9 Hz, 1H), 3.47−3.53 (m, 1H), 3.83 (dd, J = 14.6, 4.0 Hz, 1H), 4.03 (s, 2H), 6.66 (s, 1H), 7.08 (dd, J = 8.6, 8.6 Hz, 1H), 7.22−7.26 (m, 3H), 7.36−7.42 (m, 5H), 7.43−7.49 (m, 3H), 7.72 (d, J = 8.6 Hz, 2H), 7.82 (d, J = 8.0 Hz, 2H), 7.91 (d, J = 8.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 21.7, 25.8, 42.0, 42.8, 62.1, 82.6, 83.0, 89.4, 112.9, 114.3 (2C), 125.8, 126.9 (2C), 127.0 (2C), 127.2, 127.5 (2C), 127.7, 128.3, 128.7, 129.3 (2C), 130.1 (4C), 134.6, 134.7, 136.1, 137.1, 144.3, 145.6, 183.8. HRMS (FAB) calcd $C_{36}H_{30}BrN_2O_6S_2$: $(M - H)^-$ 729.0734, found $(M - H)^-$, 729.0734.

(*R*)-1-(4-Bromo-1-tosyl-1*H*-indol-3-yl)-4-[(2*R*,5*S*)-2-phenyl-3-tosyl-1,3-oxazinan-5-yl]but-3-yn-2-ol (20a). A solution of (*R*)-Alpine−Borane (0.5 M in THF, 5.1 mL, 2.57 mmol) was slowly added to ketone **16** (628 mg, 0.858 mmol) at 0 °C under argon. The resulting solution was stirred for 32 h at room temperature. After the mixture was concentrated under reduced pressure, the residue was diluted with Et_2O (24 mL). Aminoethanol (0.194 mL, 3.22 mmol) was slowly added, producing a yellow precipitate, which was removed by filtration through Celite. 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 (3:1) to give **20a** as a pale yellow amorphous solid (539 mg, 86% yield, dr = >95:5): $[\alpha]^{28}_D$ −59.1 (*c* 1.25, $CHCl_3$); IR (neat) 3507 (OH), 1374 (NSO_2), 1348 (NSO_2), 1171 (NSO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.73 (d, J = 5.2 Hz, 1H), 2.28−2.36 (m, 1H), 2.35 (s, 3H), 2.47 (s, 3H), 3.08 (dd, J = 14.3, 12.0 Hz, 1H), 3.20−3.24 (m, 2H), 3.47 (dd, J = 11.5, 11.5 Hz, 1H), 3.59−3.64 (m, 1H), 3.93 (dd, J = 14.3, 4.6 Hz, 1H), 4.53−4.60 (m, 1H), 6.68

(s, 1H), 7.09 (dd, J = 8.6, 8.6 Hz, 1H), 7.22 (d, J = 8.6 Hz, 2H), 7.30 (d, J = 8.6 Hz, 1H), 7.35−7.39 (m, 1H), 7.37 (d, J = 8.6 Hz, 2H), 7.43−7.46 (m, 5H), 7.70 (d, J = 8.6 Hz, 2H), 7.86 (d, J = 8.6 Hz, 2H), 7.93 (d, J = 8.6 Hz, 1H); ^{1}H NMR [500 MHz, $(CD_3)_2SO$] δ 2.08−2.17 (m, 1H), 2.31 (s, 3H), 2.43 (s, 3H), 2.86 (dd, J = 14.3, 12.6 Hz, 1H), 3.01−3.16 (m, 3H), 3.44 (dd, J = 11.7, 3.7 Hz, 1H), 3.79−3.86 (m, 1H), 4.37−4.42 (m, 1H), 5.48 (d, J = 5.7 Hz, 1H), 6.56 (s, 1H), 7.17 (dd, J = 8.6, 8.6 Hz, 1H), 7.27−7.33 (m, 3H), 7.34 (d, J = 8.6 Hz, 2H), 7.42 (dd, J = 8.0, 8.0 Hz, 1H), 7.46−7.53 (m, 4H), 7.66 (s, 1H), 7.78 (d, J = 8.0 Hz, 2H), 7.86 (d, J = 8.6 Hz, 2H), 7.89 (d, J = 8.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6 (2C), 25.7, 34.3, 43.9, 62.2, 63.2, 81.5, 83.0, 84.0, 112.9, 114.3, 117.3, 125.5, 126.8 (3C), 127.1 (2C), 127.5 (2C), 127.9, 128.4, 128.5, 129.2 (2C), 130.0 (4C), 134.8, 135.1, 136.3, 137.5, 144.0, 145.4. HRMS (FAB) calcd $C_{36}H_{32}BrN_2O_6S_2$: $(M - H)^-$ 731.0891, found $(M - H)^-$ 731.0889.

(2*R*,5*S*)-5-[(*R*)-4-(4-Bromo-1-tosyl-1*H*-indol-3-yl)buta-1,2-dienyl]-2-phenyl-3-tosyl-1,3-oxazinane (21a). To a stirred solution of PPh_3 (766 mg, 2.92 mmol) in THF (10 mL) was added diethyl azodicarboxylate (40% solution in toluene, 1.33 mL, 2.92 mmol) at −15 °C under argon. After stirring for 5 min at this temperature, a solution of propargylic alcohol **20a** (535 mg, 0.729 mmol) in THF (8.0 mL) was added to the reaction mixture, followed 5 min later by the addition of a solution of *o*-nitrobenzenesulfonyl hydrazide (634 mg, 2.92 mmol) in THF (9.0 mL) at −15 °C. After stirring for 2.5 h at this temperature, the mixture was allowed to warm to room temperature and stirred for further 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 **21a** as a pale yellow amorphous solid (404 mg, 77% yield, dr = 94:6): $[\alpha]^{28}_D$ −87.0 (c 1.05, $CHCl_3$); IR (neat) 1964 (C═C═C), 1378 (NSO_2), 1343 (NSO_2), 1172 (NSO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.94−2.02 (m, 1H), 2.34 (s, 3H), 2.46 (s, 3H), 2.86 (dd, J = 14.9, 12.0 Hz, 1H), 3.25 (dd, J = 11.5, 11.5 Hz, 1H), 3.39−3.44 (m, 1H), 3.49 (ddd, J = 16.2, 6.4, 2.1 Hz, 1H), 3.56 (ddd, J = 16.2, 6.3, 2.1 Hz, 1H), 3.75 (dd, J = 14.9, 4.6 Hz, 1H), 4.55−4.61 (m, 1H), 5.31−5.38 (m, 1H), 6.64 (s, 1H), 7.12 (dd, J = 8.0, 8.0 Hz, 1H), 7.22 (d, J = 8.6 Hz, 2H), 7.30 (s, 1H), 7.32−7.37 (m, 4H), 7.40−7.46 (m, 4H), 7.71 (d, J = 8.6 Hz, 2H), 7.85 (d, J = 8.6 Hz, 2H), 7.94 (d, J = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 21.6, 26.2, 31.8, 44.6, 64.2, 83.0, 88.9, 92.0, 112.9, 114.4, 121.4, 125.0, 125.5, 126.8 (2C), 127.1 (2C), 127.5 (2C), 127.7, 128.3, 128.5, 129.0 (2C), 129.9 (2C), 130.0 (2C), 134.9, 135.6, 136.4, 137.8, 143.7, 145.2, 204.4. HRMS (FAB) calcd $C_{36}H_{32}BrN_2O_5S_2$: $(M - H)^-$ 715.0941, found $(M - H)^-$ 715.0941.

***N*-[(2*S*,4*R*)-6-(4-Bromo-1-tosyl-1*H*-indol-3-yl)-2-(hydroxymethyl)hexa-3,4-dienyl]-4-methylbenzenesulfonamide (5a).** To a stirred mixture of **21a** (400 mg, 0.557 mmol, dr = 94:6) in $MeOH/CH_2Cl_2$ (20 mL, 1:1) was added *p*-toluenesulfonic acid monohydrate (159 mg, 0.836 mmol) at room temperature. After stirring for 3.5 h at 50 °C, concentration under reduced pressure gave an oily residue. The residue was dissolved in EtOAc, 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 (3:2) to give **5a** as a white amorphous solid (299 mg, 85% yield, dr = 94:6): $[\alpha]^{28}_D$ −50.6 (c 1.15, $CHCl_3$); IR (neat) 3313 (OH), 1963 (C═C═C), 1413 (NSO_2), 1372 (NSO_2), 1172 (NSO_2), 1157 (NSO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.77 (t, J = 6.3 Hz, 1H), 2.21−2.29 (m, 1H), 2.35 (s, 3H), 2.43 (s, 3H), 2.79−2.90 (m, 2H), 3.39 (ddd, J = 10.3, 6.3, 5.7 Hz, 1H), 3.49 (ddd, J = 10.3, 6.3, 4.5 Hz, 1H), 3.56−3.69 (m, 2H), 4.68 (t, J = 6.6 Hz, 1H), 4.92−4.97 (m, 1H), 5.46−5.52 (m, 1H), 7.09 (dd, J = 8.0, 8.0 Hz, 1H), 7.23 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 8.0 Hz, 1H), 7.42 (s, 1H), 7.71 (d, J = 8.0 Hz, 2H), 7.73 (d, J = 8.0 Hz, 2H), 7.92 (d, J = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5 (2C), 26.2, 40.7, 44.2, 63.4, 90.3, 92.0, 112.8, 114.5, 121.3, 125.2, 125.5, 126.8 (2C), 127.0 (2C), 127.7, 128.6, 129.7 (2C), 130.0 (2C), 134.8, 136.4, 136.9, 143.4, 145.3, 204.7. HRMS (FAB) calcd $C_{29}H_{28}BrN_2O_5S_2$: $(M - H)^-$ 627.0628, found $(M - H)^-$ 627.0627.

Determination of Relative Configuration of the Allenamide 5a: Synthesis of the Authentic Sample *rac*-5a by Desilylation of the Known Allenamide *rac*-24. To a stirred solution of *rac*-**24a**[14] (2.6 mg, 0.0033 mmol) in THF (0.30 mL) was added TBAF (1.00 M solution in THF; 33 μL, 0.033 mmol) at 0 °C. The mixture was stirred for 30 min at room temperature. Concentration under reduced pressure gave an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane−EtOAc (3:2) to give *rac*-**5a** as a white amorphous solid (1.9 mg, 91% yield).

(*S*)-1-(4-Bromo-1-tosyl-1*H*-indol-3-yl)-4-[(2*R*,5*S*)-2-phenyl-3-tosyl-1,3-oxazinan-5-yl]but-3-yn-2-ol (20b). A solution of (*S*)-Alpine-Borane (0.5 M in THF, 0.82 mL, 0.137 mmol) was slowly added to ketone **16** (100 mg, 0.410 mmol) at 0 °C under argon. The resulting solution was stirred for 33 h at room temperature. After the mixture was concentrated under reduced pressure, the residue was diluted with Et_2O (3.8 mL). Aminoethanol (0.031 mL, 0.514 mmol) was slowly added, producing a yellow precipitate that was removed by filtration through Celite. 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 (3:1) to give **20b** as a pale yellow amorphous solid (69.5 mg, 69% yield, dr = >95:5): $[\alpha]^{28}_D$ −38.2 (c 0.84, $CHCl_3$); IR (neat) 3501 (OH), 1373 (NSO_2), 1347 (NSO_2), 1170 (NSO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.73 (d, J = 5.2 Hz, 1H), 2.28−2.36 (m, 1H), 2.35 (s, 3H), 2.46 (s, 3H), 3.10 (dd, J = 14.3, 12.0 Hz, 1H), 3.18 (dd, J = 14.6, 6.0 Hz, 1H), 3.25 (dd, J = 14.6, 6.6 Hz, 1H), 3.44 (dd, J = 11.5, 11.5 Hz, 1H), 3.58 (dd, J = 11.5, 4.0 Hz, 1H), 3.95 (dd, J = 14.3, 2.9 Hz, 1H), 4.54−4.60 (m, 1H), 6.68 (s, 1H), 7.09 (dd, J = 8.0, 8.0 Hz, 1H), 7.21 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 8.0 Hz, 1H), 7.35−7.41 (m, 3H), 7.43−7.46 (m, 5H), 7.69 (d, J = 8.0 Hz, 2H), 7.87 (d, J = 8.0 Hz, 2H), 7.93 (d, J = 8.0 Hz, 1H); ^{1}H NMR [500 MHz, $(CD_3)_2SO$] δ 2.06−2.15 (m, 1H), 2.31 (s, 3H), 2.42 (s, 3H), 2.85 (dd, J = 14.9, 12.0 Hz, 1H), 3.01 (dd, J = 10.9, 7.4 Hz, 1H), 3.11−3.18 (m, 2H), 3.49 (dd, J = 10.9, 4.0 Hz, 1H), 3.81 (dd, J = 14.9, 4.6 Hz, 1H), 4.36−4.41 (m, 1H), 5.48 (d, J = 5.7 Hz, 1H), 6.57 (s, 1H), 7.18 (dd, J = 8.6, 8.6 Hz, 1H), 7.29−7.35 (m, 5H), 7.41 (dd, J = 8.0, 8.0 Hz, 1H), 7.45−7.53 (m, 4H), 7.68 (s, 1H), 7.78 (d, J = 8.6 Hz, 2H), 7.87 (d, J = 8.6 Hz, 2H), 7.89 (d, J = 8.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6 (2C), 25.7, 34.3, 43.9, 62.2, 63.2, 81.4, 83.0, 84.0, 112.9, 114.3, 117.3, 125.4, 126.8 (3C), 127.1 (2C), 127.5 (2C), 127.9, 128.4, 128.5, 129.1 (2C), 130.0 (2C), 130.1 (2C), 134.8, 135.1, 136.2, 137.5, 144.0, 145.4. HRMS (FAB) calcd $C_{36}H_{32}BrN_2O_6S_2$: $(M - H)^-$ 731.0891, found $(M - H)^-$ 731.0891.

(2*R*,5*S*)-5-[(*S*)-4-(4-Bromo-1-tosyl-1*H*-indol-3-yl)buta-1,2-dienyl]-2-phenyl-3-tosyl-1,3-oxazinane (21b). By a procedure identical with that described for synthesis of **21a** from **20a**, the propargylic alcohol **20b** (135 mg, 0.184 mmol) was converted into **21b** as a pale yellow amorphous solid (80.5 mg, 61% yield, dr = 94:6): $[\alpha]^{28}_D$ +20.3 (c 0.78, $CHCl_3$); IR (neat) 1964 (C═C═C), 1374 (NSO_2), 1344 (NSO_2), 1172 (NSO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.88−1.96 (m, 1H), 2.30 (s, 3H), 2.46 (s, 3H), 2.87 (dd, J = 14.6, 12.0 Hz, 1H), 3.10 (dd, J = 11.2, 11.2 Hz, 1H), 3.12−3.17 (m, 1H), 3.48 (ddd, J = 16.6, 6.3, 3.0 Hz, 1H), 3.60 (ddd, J = 16.6, 6.9, 2.9 Hz, 1H), 3.75 (dd, J = 14.6, 4.3 Hz, 1H), 4.41−4.46 (m, 1H), 5.32−5.38 (m, 1H), 6.63 (s, 1H), 7.12 (dd, J = 8.6, 8.6 Hz, 1H), 7.20 (d, J = 8.6 Hz, 2H), 7.31−7.38 (m, 5H), 7.39−7.45 (m, 4H), 7.70 (d, J = 8.6 Hz, 2H), 7.82 (d, J = 8.6 Hz, 2H), 7.95 (d, J = 8.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 21.6, 26.1, 32.0, 44.4, 64.3, 83.0, 89.0, 92.2, 112.9, 114.4, 121.3, 125.1, 125.5, 126.8 (2C), 127.1 (2C), 127.5 (2C), 127.8, 128.3, 128.6, 129.0 (2C), 129.9 (4C), 134.9, 135.6, 136.5, 137.8, 143.7, 145.2, 204.6. HRMS (FAB) calcd $C_{36}H_{32}BrN_2O_5S_2$: $(M - H)^-$ 715.0941, found $(M - H)^-$ 715.0938.

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***N*-[(2*S*,4*S*)-6-(4-Bromo-1-tosyl-1*H*-indol-3-yl)-2-(hydroxymethyl)hexa-3,4-dienyl]-4-methylbenzenesulfonamide (5b).** By a procedure identical with that described for synthesis of **5a** from **21a**, the allene **21b** (77.7 mg, 0.108 mmol, dr = 94:6) was converted into **5b** as a white amorphous solid (58.5 mg, 86% yield, dr = 94:6): $[\alpha]^{28}_{D}$ +48.8 (*c* 1.57, $CHCl_3$); IR (neat) 3292 (OH), 1965 (C═C═C), 1412 (NSO_2), 1372 (NSO_2), 1172 (NSO_2), 1157 (NSO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.85−1.91 (m, 1H), 2.17−2.26 (m, 1H), 2.35 (s, 3H), 2.42 (s, 3H), 2.88 (ddd, *J* = 12.0, 6.3, 5.7 Hz, 1H), 2.96 (ddd, *J* = 12.0, 6.3, 5.7 Hz, 1H), 3.33−3.46 (m, 2H), 3.59 (ddd, *J* = 16.5, 5.7, 2.9 Hz, 1H), 3.66 (ddd, *J* = 16.5, 6.4, 2.1 Hz, 1H), 4.79 (t, *J* = 6.3 Hz, 1H), 4.87−4.92 (m, 1H), 5.45−5.52 (m, 1H), 7.10 (dd, *J* = 8.6, 8.6 Hz, 1H), 7.23 (d, *J* = 8.6 Hz, 2H), 7.30 (d, *J* = 8.6 Hz, 2H), 7.32 (d, *J* = 8.6 Hz, 1H), 7.42 (s, 1H), 7.72 (d, *J* = 8.6 Hz, 2H), 7.73 (d, *J* = 8.6 Hz, 2H), 7.94 (d, *J* = 8.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 21.6, 26.1, 40.8, 44.1, 63.5, 90.3, 92.0, 112.9, 114.4, 121.3, 125.2, 125.5, 126.9 (2C), 127.0 (2C), 127.7, 128.6, 129.8 (2C), 130.0 (2C), 134.9, 136.5, 136.9, 143.5, 145.3, 204.8. HRMS (FAB) calcd $C_{29}H_{28}BrN_2O_5S_2$: $(M - H)^-$ 627.0628, found $(M - H)^-$ 627.0630.

[(6a*R*,9*S*)-4,7-Ditosyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinolin-9-yl]methanol (4a). To a stirred mixture of allenamide **5a** (248 mg, 0.39 mmol, dr = 94:6) in DMF (8.0 mL) were added $Pd(PPh_3)_4$ (22.8 mg, 0.020 mmol) and K_2CO_3 (162 mg, 1.17 mmol) at room temperature under argon, and the mixture was stirred for 2.5 h at 100 °C. Concentration under reduced pressure gave an oily residue. The residue was dissolved in EtOAc, washed with saturated NH_4Cl, H_2O, and brine, and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give a brown oil, which was purified by flash chromatography over silica gel with *n*-hexane−EtOAc (1:1), followed by flash chromatography over Chromatorex with *n*-hexane−EtOAc (1:1 to 1:2) to give **4a** as a pale brown amorphous solid (162 mg, 76% yield, dr = 92:8). The pure diastereomer **4a** was isolated by PTLC with *n*-hexane−EtOAc−MTBE (1:1:1): $[\alpha]^{28}_{D}$ −129.1 (*c* 0.38, $CHCl_3$); IR (neat) 3523 (OH), 1597 (C═C), 1357 (NSO_2), 1342 (NSO_2), 1178 (NSO_2), 1155 (NSO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.26−2.33 (m, 1H), 2.35 (s, 3H), 2.40 (s, 3H), 2.87−2.96 (m, 2H), 3.31 (dd, *J* = 14.3, 5.2 Hz, 1H), 3.51−3.63 (m, 2H), 4.08 (dd, *J* = 14.3, 5.2 Hz, 1H), 4.67−4.72 (m, 1H), 6.13 (s, 1H), 7.17 (d, *J* = 8.0 Hz, 1H), 7.20−7.29 (m, 6H), 7.68 (d, *J* = 8.0 Hz, 2H), 7.77 (d, *J* = 8.0 Hz, 2H), 7.79 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5 (2C), 29.7, 37.1, 42.3, 53.4, 64.2, 112.8, 115.6, 117.5, 120.5, 123.7, 125.7, 126.8 (4C), 128.3, 129.8 (2C), 129.9 (2C), 130.1, 133.4, 134.1, 135.4, 138.0, 143.4, 144.9; HRMS (FAB) calcd $C_{29}H_{29}N_2O_5S_2$: $(M + H)^+$ 549.1518, found $(M + H)^+$ 549.1516.

Determination of Relative Configuration of the Alcohol 4a: Synthesis of the Authentic Sample *rac*-4a by Desilylation of the Known Tetracyclic Indole *rac*-25. To a stirred solution of *rac*-**25a**[14] (2.6 mg, 0.0037 mmol) in THF (0.30 mL) was added TBAF (1.00 M solution in THF; 37 μL, 0.037 mmol) at 0 °C. The mixture was stirred for 30 min at room temperature. Concentration under reduced pressure gave an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane−EtOAc (1:1) to give *rac*-**4a** as a white amorphous solid (2.2 mg, quant).

[(6a*S*,9*S*)-4,7-Ditosyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinolin-9-yl]methanol (4b). By a procedure identical with that described for synthesis of **4a** from **5a**, the allenamide **5b** (25 mg, 0.040 mmol, dr = 94:6) was converted into **4b** as a pale brown amorphous solid (9.4 mg, 43% yield, dr = 69:31). The pure diastereomer **4b** was isolated by PTLC with *n*-hexane−EtOAc−MTBE (1:1:1): $[\alpha]^{28}_{D}$ +6.0 (*c* 0.19, $CHCl_3$); IR (neat) 3560 (OH), 1597 (C═C), 1359 (NSO_2), 1335 (NSO_2), 1178 (NSO_2), 1155 (NSO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.35 (s, 3H), 2.35−2.38 (m, 1H), 2.46 (s, 3H), 2.55−2.61 (m, 1H), 2.72 (ddd, *J* = 14.3, 12.0, 1.7 Hz, 1H), 3.00 (dd, *J* = 14.3, 5.2 Hz, 1H), 3.08 (dd, *J* = 13.7, 2.9 Hz, 1H), 3.52 (ddd, *J* = 12.0, 10.3, 5.7 Hz, 1H), 3.66 (ddd, *J* = 12.0, 7.4, 5.2 Hz, 1H), 4.09 (d, *J* = 13.7 Hz, 1H), 4.77−4.82 (m, 1H), 6.30 (d, *J* = 5.7 Hz, 1H), 7.14 (d, *J* = 1.7 Hz, 1H), 7.17−7.30 (m, 4H), 7.35 (d, *J* = 8.6 Hz, 2H), 7.74 (d, *J* = 8.6 Hz, 2H), 7.77 (d, *J* = 8.6 Hz, 1H), 7.78 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5 (2C), 27.3, 38.7, 39.8, 53.2, 61.6, 112.8, 115.8, 117.0, 120.5, 122.5, 125.9, 126.7 (4C), 128.0, 129.9 (4C), 130.2, 133.3, 134.8, 135.4, 138.6, 143.6, 144.9; HRMS (FAB) calcd $C_{29}H_{29}N_2O_5S_2$: $(M + H)^+$ 549.1518, found $(M + H)^+$ 549.1519.

(+)-Isolysergol (3). To a stirred solution of **4a** (20 mg, 0.036 mmol, dr = 92:8) in THF (0.50 mL) was added sodium naphthalenide (0.67 M solution in THF; 0.82 mL, 0.55 mmol)[40] at −78 °C under argon. The mixture was stirred for 10 min at this temperature and quenched with saturated NH_4Cl. The mixture was made basic with saturated $NaHCO_3$. The whole was extracted with EtOAc. The extract was washed with brine and dried over $MgSO_4$. Concentration of the filtrate under reduced pressure gave a crude amine, which was used without further purification. To a stirred solution of this amine in MeOH (2.6 mL) were added formalin (0.028 mL, 0.36 mmol), $NaBH_3CN$ (22.6 mg, 0.36 mmol), and AcOH (47 μL) at room temperature. After stirring for 1 h at this temperature, the mixture was quenched with saturated $NaHCO_3$. After MeOH was removed under reduced pressure, 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 a yellow solid, which was purified by PTLC (Chromatorex) with *n*-hexane−EtOAc (1:10) to give isolysergol (**3**) as a pale brown solid (4.2 mg, 46% yield, 99% ee [HPLC, Chiralcel-OD column eluting with 10:90 *n*-hexane/*i*-PrOH at 0.5 mL/min, t_1 = 9.50 min (minor isomer), t_2 = 12.98 min (major isomer)][3o]). $[\alpha]^{28}_{D}$ +200.3 (*c* 0.37, pyridine) [lit. $[\alpha]^{20}_{D}$ +228 (*c* 0.40, pyridine)].[37] All spectral data were in agreement with those of our previous report.[14]

Methyl (6a*R*,9*S*)-4,7-Ditosyl-4,6,6a,7,8,9-hexahydroindolo-[4,3-*fg*]quinoline-9-carboxylate (22a). To a stirred solution of **4a** (40 mg, 0.072 mmol, dr = 92:8) in CH_2Cl_2 (3.2 mL) was added Dess−Martin periodinane (124 mg, 0.29 mmol) at 0 °C. After stirring for 30 min at this temperature, the mixture was warming to room temperature. The mixture was stirred for further 1.5 h at this temperature and filtrated through a short pad of SiO_2 with EtOAc. The filtrate was concentrated under reduced pressure to give a crude aldehyde, which was used without further purification. To a stirred mixture of the crude aldehyde and 2-methylbut-2-ene (0.44 mL, 4.32 mmol) in a mixed solvent of THF (1.5 mL) and *t*-BuOH (1.5 mL) were added a solution of $NaClO_2$ (62.4 mg, 0.69 mmol) and NaH_2PO_4 (82.8 mg, 0.69 mmol) in H_2O (0.71 mL) at room temperature. After stirring for 1.5 h at room temperature, brine was added to the mixture. The whole was extracted with EtOAc. The extract was washed with brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give a crude carboxylic acid, which was purified by flash chromatography over silica gel with a gradient solvent [*n*-hexane−EtOAc (1:2) to EtOAc−MeOH (9:1)]. To a stirred solution of this carboxylic acid in a mixed solvent of toluene (1.5 mL) and MeOH (0.79 mL) was added $TMSCHN_2$ (2.00 M solution in Et_2O; 0.36 mL, 0.72 mmol) at 0 °C. The mixture was stirred for 20 min at room temperature. Concentration under pressure gave an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane−EtOAc (3:1) to give **22a** as a pale yellow amorphous solid (26.5 mg, 64% yield, dr = >95:5). Its purity was confirmed by ^{1}H NMR analysis. $[\alpha]^{25}_{D}$ −93.2 (*c* 0.95, $CHCl_3$). All spectral data were in agreement with those of our previous report.[14]

(+)-Methyl Isolysergate (23a) and (+)-Methyl Lysergate (23b). The preparation of (+)-methyl isolysergate (**23a**) and (+)-methyl lysergate (**23b**) from **22a** was carried out according to our previous report:[14] To a stirred solution of **22a** (26 mg, 0.045 mmol) in THF (1.4 mL) was added sodium naphthalenide (0.67 M solution in THF; 0.67 mL, 0.45 mmol)[40] at −78 °C under argon. The mixture was stirred for 6 min at this temperature and quenched with saturated NH_4Cl. The mixture was made basic with saturated $NaHCO_3$. The

whole was extracted with EtOAc. The extract was washed with brine and dried over $MgSO_4$. Concentration of the filtrate under reduced pressure gave a crude amine, which was used without further purification. To a stirred solution of this amine in MeOH (3.0 mL) were added AcOH (47 μL), $NaBH_3CN$ (14.1 mg, 0.23 mmol), and formalin (17.7 μL, 0.23 mmol) at room temperature. After stirring for 2 h at this temperature, the mixture was quenched with saturated $NaHCO_3$. The mixture was concentrated under pressure, and 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 a yellow solid, which was purified by flash chromatography over silica gel with *n*-hexane−EtOAc (1:3 to 1:10) to give **23** as a yellow solid (8.2 mg, 65% yield, **a**:**b** = 33:67). All spectral data were in agreement with those of our previous report.[14]

(+)-Lysergol (2) and (+)-Isolysergol (3). To a stirred solution of **23** (8.2 mg, 0.029 mmol, **a**:**b** = 33:67) in THF (0.5 mL) was added $LiAlH_4$ (5.5 mg, 0.145 mmol) at 0 °C. The mixture was stirred for 10 min at this temperature and quenched with saturated Na_2SO_4. The whole was extracted with EtOAc. The extract was washed with brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give a yellow solid, which was purified by PTLC (Chromatorex) with EtOAc−MeOH (9:1) to give isolysergol (**3**) as a pale brown solid (1.8 mg, 24% yield, 97% ee), and lysergol (**2**) as a pale brown solid (3.6 mg, 49% yield, 98% ee [HPLC, Chiralcel-OD column eluting with 70:30 *n*-hexane/EtOH at 0.5 mL/min, t_1 = 13.19 min (minor isomer), t_2 = 17.64 min (major isomer)]). $[\alpha]^{26}_D$ +40.9 (*c* 0.32, pyridine) [lit. $[\alpha]^{20}_D$ +54 (*c* 0.40, pyridine)].[37] All spectral data were in agreement with those of our previous report.[14]

(+)-Lysergic Acid (1). The preparation of lysergic acid (**1**) was carried out according to the method of Hendrickson[3i] and Szántay:[3j] To solution of diastereomixture of **23** (20.0 mg, 0.071 mmol, **a**:**b** = 33:67) in EtOH (0.69 mL) was added 1 N NaOH (0.69 mL). The reaction mixture was stirred for 2 h at 35 °C. Next, 0.1 N HCl solution was used to carefully adjust the pH to 6.2, and the mixture was stirred at 0 °C for further 2 h while a solid material was formed. The precipitate was filtered off and washed with cold water and acetone to give (+)-lysergic acid (**1**) as a pale brown solid (10.2 mg, 54% yield): mp 220−223 °C dec (lit. mp 230−240 °C dec);[3j] $[\alpha]^{26}_D$ +36.1 (*c* 0.14, pyridine) [lit. $[\alpha]^{20}_D$ +40 (*c* 0.50, pyridine)].[3j] All spectral data were in agreement with those of our previous report.[14]

Determination of Optical Purity of Lysergic Acid (1). To a stirred suspension of lysergic acid (**1**) (2.5 mg, 0.0093 mmol) in a mixed solvent of EtOH (0.5 mL) and benzene (0.25 mL) was added $TMSCHN_2$ (2.00 M solution in Et_2O; 0.047 mL, 0.093 mmol) at 0 °C. The mixture was stirred for 10 min at room temperature. Concentration under pressure gave an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane−EtOAc (1:3 to 1:10) to give **23** as a pale yellow solid (2.5 mg, 95% yield, **a**:**b** = 15:85, >95% ee (**23a**), 96% ee (**23b**) [HPLC, Chiralcel-OD column eluting with 80:20 *n*-hexane/EtOH at 0.5 mL/min, t_1 = 16.88 min (methyl lysergate, minor isomer), t_2 = 18.67 min (methyl isolysergate, minor isomer), t_3 = 25.08 min (methyl lysergate, major isomer), t_4 = 27.54 min (methyl isolysergate, major isomer)]).

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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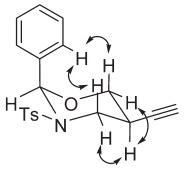

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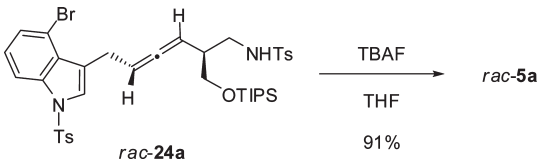
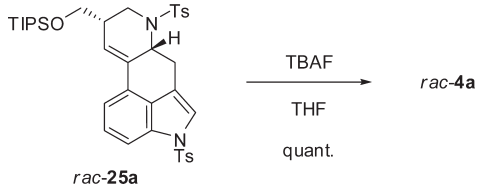
(32) The relative configuration of allenic amide **5a** was confirmed by comparison with the authentic sample *rac*-**5a** prepared from the known allenic amide **24a**, which in turn was obtained through an Au-catalyzed Claisen rearrangement of the corresponding propargyl vinyl ether (see ref 14).



(33) The relative configuration of **4a** was confirmed by comparison with the authentic sample prepared from the known compound **25a** (see ref 14).



(34) We cannot rule out other factors for rationalization of the observed selectivities. For example, the reactive conformer as depicted in **E** might have better orbital alignment for anti-addition of the amine nucleophile to the allenic moiety activated by Pd(II) than in *epi*-**E**, thus leading to a selective formation of the desired product **4a**. Further investigations on the stereoselectivities of these cyclization reactions are currently underway in our laboratory.

(35) The reproducibility of the oxidation reaction was significantly dependent on the purity of the Dess−Martin reagent.

(36) Separation of the diastereomer at this step is important for the preparation of lysergic acid (**1**) in high ee, because the transformation of **23** to **1** accompanying isomerization relies on the chirality at C-5.

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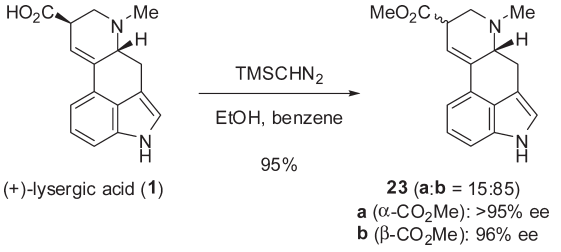

(39) Lysergic acid is known to racemize under harsh basic conditions [$Ba(OH)_2$ aq, sealed tube, 150 °C, 4 h]; see: (a) Smith, S.; Timmis, G. M. *J. Chem. Soc.* **1936**, 1440–1444. (b) Moldvai, I.; Gács-Baitz, E.; Temesvári-Major, E.; Russo, L.; Pápai, I.; Rissanen, K.; Szárics, É.; Kardos, J.; Szántay, C. *Heterocycles* **2007**, *71*, 1075–1095.

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