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ORIGINAL ARTICLE

Total synthesis of (+)-lysergic acid

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A total synthesis of (+)-lysergic acid, which features the C–C bond formation between C10 and C11 via cleavage of an aziridine ring, was accomplished.
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INTRODUCTION

Ergot alkaloids are a class of pharmacologically important natural products that display a wide range of biological activities.[1,2] Alkaline hydrolysis of ergot alkaloids yields lysergic acid (**1**; Figure 1), which is characterized by a unique tetracyclic ergoline skeleton containing a tetrahydropyridine and a [*cd*]-fused indole. These unique structural features have attracted a great deal of attention of synthetic chemists, and a number of total synthesis and synthetic studies toward lysergic acid have been reported to date.[3–30] The C–C bond formation between C10 and C11 is a central issue in the synthesis of lysergic acid. A variety of key reactions, including the Friedel–Crafts reaction,[3,9,10] the addition to a benzyne,[4] the Suzuki–Miyaura coupling,[15,27,28] the aminopalladation reaction[17,20,21] and the Heck reaction,[22–24,29] have been used toward this end. Herein, we disclose a total synthesis of (+)-lysergic acid via a novel C–C bond formation reaction between C10 and C11, which involves the cleavage of an aziridine ring.

RESULTS AND DISCUSSION

In preliminary studies we prepared indole **2** from D-tryptophan and attempted the crucial C–C bond formation reaction (Scheme 1). When **2** was treated with boron trifluoride in dichloromethane at 0 °C, the reaction provided a complex mixture and the desired product **3** could not be obtained. The planar nature of the sp^2 carbon at the 3-position of the indole core appeared to inhibit the orbital overlap between the aziridine moiety and the 4-position of the indole to form the C–C bond. The undesired reaction between the aziridine moiety and the electron-rich 3-position of the indole might have occurred, leading to the decomposition of the substrate. We therefore decided to use an indoline as a substrate in place of indole **2**. Indolines such as **4** contain three stereogenic centers, one at the 3-position of the indoline and two on the aziridine ring. After screening of a combination of stereoisomers, we found that (3*R*,5*R*,10*R*)-*trans*-aziridine **4** was optimal for synthesizing (+)-lysergic acid. Reaction of (3*S*,5*R*,10*R*)-*trans*-aziridine did not provide the desired product at all. Reactions of *cis*-aziridines produced the desired products in low yields or proceeded more slowly.

The stereogenic centers suitable for the synthesis of (+)-lysergic acid were constructed by means of diastereoselective reactions controlled by an appropriate choice of chiral auxiliaries (Scheme 2). The installation of (*R*)-4-benzyloxazolidin-2-one (**6**) as a chiral auxiliary into (2-bromophenyl)acetic acid (**5**), followed by diastereoselective allylation,[31] afforded **7**, which was reduced with lithium aluminum hydride to furnish alcohol **8**. A Mitsunobu reaction[32] of **8** with *N*-Boc-tosylamide and subsequent removal of the Boc group with trifluoroacetic acid (TFA) gave tosylamide **9**. The copper-mediated aryl amination proceeded smoothly at room temperature to produce indoline **10**.[33,34] A two-step oxidative manipulation of the terminal olefin moiety in **10** afforded carboxylic acid **11**, onto which (*R*)-4-benzyloxazolidin-2-one (**6**) was installed via the corresponding mixed anhydride, giving acyloxazolidinone **12**. Formation of a titanium enolate from **12** followed by the addition of aldehyde **13** and hexamethylphosphoric triamide caused a diastereoselective aldol reaction to furnish *syn*-adduct **14** in 63% yield.[35,36] Hydrazinolysis of **14** gave the corresponding hydrazide, which was then reacted with *tert*-butyl nitrite in the presence of boron trifluoride to give an acyl azide. Upon heating in toluene, the acyl azide underwent Curtius rearrangement, and the resulting isocyanate was intramolecularly trapped by the hydroxy group to afford oxazolidinone **15**.

Having constructed the requisite stereogenic centers, we next focused on the crucial C–C bond formation (Scheme 3). After introducing a *p*-nosyl group[37–39] at the nitrogen atom in the oxazolidinone, the resulting product **16** was treated with lithium hydroxide in aqueous tetrahydrofuran to cleave the oxazolidinone ring, yielding hydroxy-nosylamide **17**. An intramolecular Mitsunobu reaction of **17** proceeded smoothly with inversion of the stereochemistry to furnish *trans*-aziridine **18**. Upon treatment of **18** with boron trifluoride in dichloromethane, the requisite C–C bond formation reaction with cleavage of the aziridine ring occurred in a stereospecific manner to give **19** in 69% yield. The reaction of **18** with a Brønsted acid; for example, TsOH or CSA, produced **19** in ~20% yield. Using $Cu(OTf)_2$ as a Lewis acid did not provide **19**.

The tricyclic compound **19** thus obtained was converted into lysergic acid as shown in Scheme 4. After cleavage of the silyl ether

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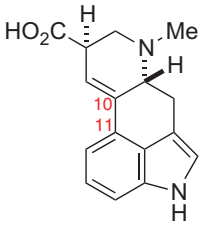
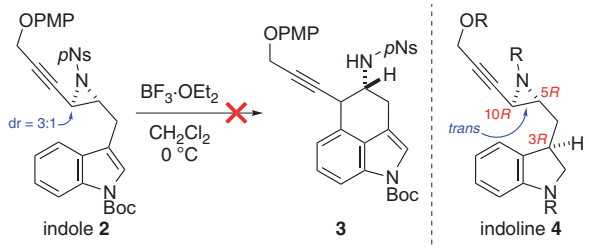
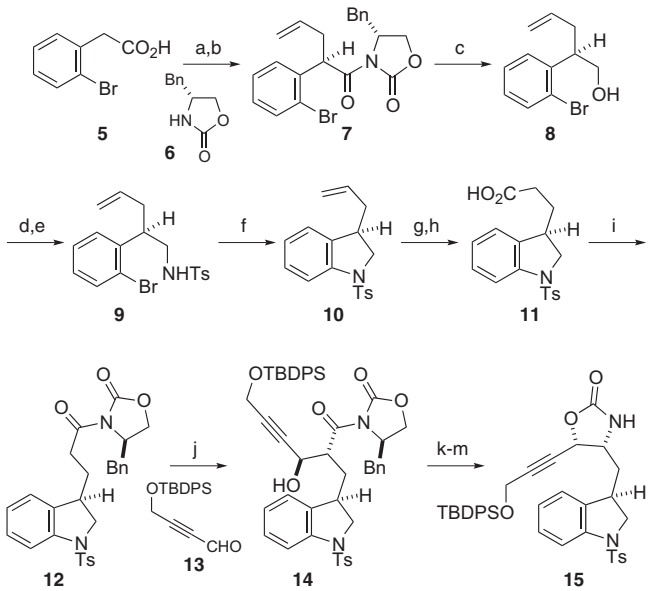


(+)-lysergic acid (**1**)

Figure 1 Structure of (+)-lysergic acid.



Scheme 1 Attempted formation of the C–C bond between C10 and C11 by using indole **2**.



Scheme 2 Reagents and conditions: (a) PivCl, Et_3N, tetrahydrofuran (THF), 0 °C; (*R*)-4-benzyloxazolidin-2-one (**6**), *n*BuLi, THF, –78 °C to room temperature (rt), 78%; (b) NaHMDS, allyl bromide, toluene-THF, –78 °C to rt, 74%, dr = 13.6:1; (c) $LiAlH_4$, THF, 0 °C, 85%; (d) TsNHBoc, DIAD, Ph_3P, toluene-THF, 80 °C, 99%; (e) trifluoroacetic acid (TFA), CH_2Cl_2, rt; (f) CuI, CsOAc, DMSO, rt, 58% (two steps); (g) $(Sia)_2BH$, THF, 0 °C to rt, 97%; (h) Jones reagent, acetone, 0 °C, 77%; (i) PivCl, Et_3N, THF, 0 °C; (*R*)-4-benzyloxazolidin-2-one (**6**), *n*BuLi, THF, –78 °C to rt, 100%; (j) $TiCl_4$, iPr_2NEt, CH_2Cl_2, –78 °C; aldehyde **13**, hexamethylphosphoric triamide (HMPA), –78 °C to rt, 63%; (k) NH_2NH_2, THF, rt; (l) *t*BuONO, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C; (m) toluene, 110 °C, 63% (three steps).

with tetra-*n*-butylammonium fluoride, the resulting propargyl alcohol was subjected to the palladium-catalyzed hydrostannylation to afford **20** in 60% yield.[40–44] The regioisomer was also obtained in 9% yield. An intramolecular Mitsunobu reaction of **20** constructed the tetrahydropyridine ring. Cleavage of the nosyl group in **21** with thioglycolic acid liberated a secondary amine, which was methylated with formalin and sodium cyanoborohydride. The tosyl group in **22** was subsequently removed by treatment with sodium naphthalenide, and the resulting unprotected indoline was oxidized with benzeneseleninic anhydride to give an indole,[45–47] which was protected with a Boc group to furnish **23**. Iodination of the alkenylstannane moiety with *N*-iodosuccinimide gave alkenyl iodide **24**, which, upon treatment with carbon monoxide in the presence of a palladium catalyst, underwent carbonylation to give an epimeric mixture of esters **25**. During the carbonylation, isomerization of the C–C double bond was observed. Cleavage of the *tert*-butyl group in **25** by treatment with TFA was followed by decarboxylation of the resulting carbamic acid by heating with pyridine in acetonitrile at 50 °C. Finally, alkaline hydrolysis of the ester moiety afforded (+)-lysergic acid (**1**).

In conclusion, we have accomplished a total synthesis of lysergic acid, in which the C–C bond formation between C10 and C11 could be achieved via facile cleavage of an aziridine ring.

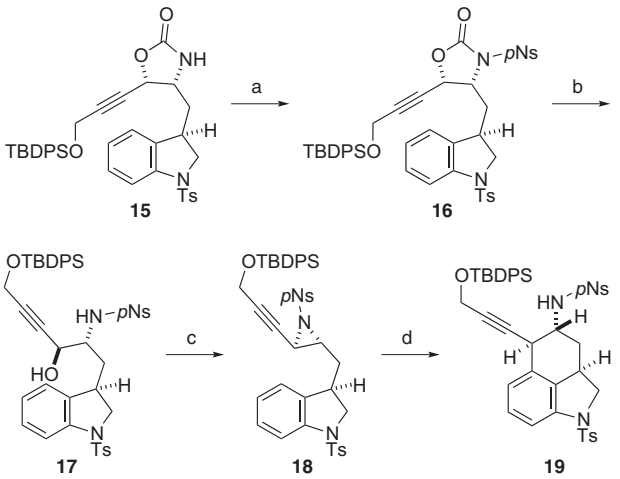
EXPERIMENTAL PROCEDURES

General remarks

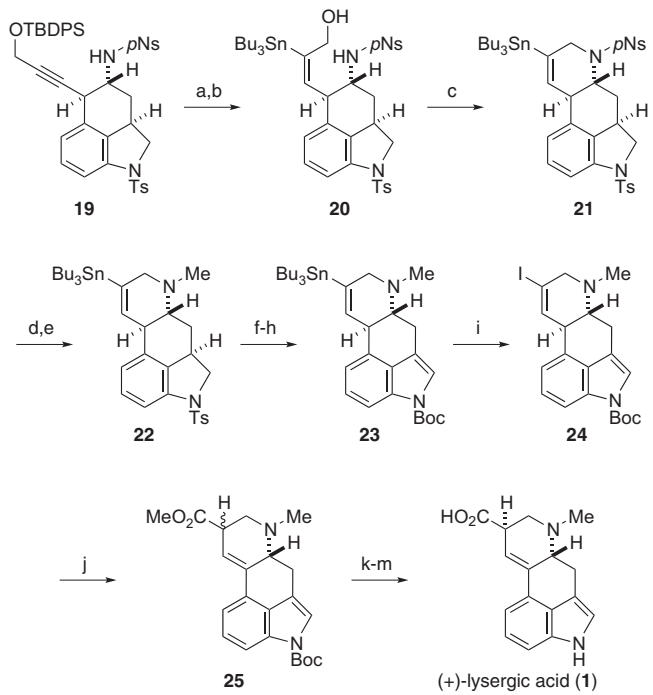
NMR (^1H NMR, 500, 400 MHz and ^{13}C NMR, 125, 100 MHz) spectra were determined on JEOL-ECX500 and JEOL-ECS400 instrument (JEOL, Ltd., Akishima, Japan). Chemical shifts for ^1H NMR are reported in p.p.m. downfields from tetramethylsilane (δ), chloroform in deuteriochloroform or methanol in methanol-d_4 as the internal standard. Coupling constants are in hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; br = broad. Chemical shifts for ^{13}C NMR were reported in p.p.m. relative to the centerline of a triplet at 77.0 p.p.m. for deuteriochloroform. IR spectra were recorded on JASCO FT/IR-4100 and FT/IR 410 Fourier Transform Infrared Spectrophotometer (JASCO Corporation, Hachioji, Japan), and are reported in wavenumbers (cm^{-1}). HR-MS were obtained on JEOL JMS-T100LC AccuTOF Spectrometer (JEOL, Ltd.) and JEOL JMS-T100LP AccuTOF LC-plus either in positive ESI method using TFA Na as the internal standard or positive direct analysis on real-time method using polyethylene glycol (PEG) as the internal standard. Melting points were measured on a Yamato Micro Melting Point Apparatus MP-21 (Yamato Scientific Co., Ltd., Tokyo, Japan). All non-aqueous reactions were carried out under an inert atmosphere of argon in oven-dried glassware unless otherwise noted. Dehydrated diethyl ether, tetrahydrofuran, methylene chloride and toluene were obtained by passing commercially available predried, oxygen-free formulations through activated alumina columns. Dehydrated *N*,*N*-dimethylformamide was purchased from Kanto Chemicals and stored over activated MS4A. Dehydrated methanol, ethanol and acetonitrile were also purchased from Kanto Chemicals (Tokyo, Japan) and stored over activated MS3A. All other reagents were commercially available and used without further purification. Analytical TLC was performed on Merck precoated analytical plates, 0.25 mm thick, silica gel 60F254. Preparative flash chromatography was performed using Silica Gel 60 (spherical, 40–100 mm) purchased from Kanto Chemical.

(*R*)-4-benzyl-3-((*R*)-2-(2-bromophenyl)pent-4-enoyl)oxazolidin-2-one (7)

To a solution of 2-bromophenylacetic acid (**5**, 25.22 g, 117.2 mmol) in tetrahydrofuran (250 ml) were added triethylamine (17.96 ml, 128.2 mmol) and pivaloyl chloride (15.84 ml, 128.9 mmol) at 0 °C. After forming white suspension, the reaction mixture was cooled to –78 °C. In the other reaction flask (*R*)-4-benzyl-2-oxazolidinone (**6**, 23.88 g, 134.8 mmol) was dissolved in tetrahydrofuran (220 ml) and cooled at –78 °C. To this solution was added *n*-butyllithium (2.66 M in hexane, 50.7 ml, 134.8 mmol) at –78 °C, and then the reaction mixture was allowed to warm up to 0 °C, which was added to the white suspended solution via cannular for 20 min at –78 °C. After stirring at room temperature for 2 h, the reaction mixture was quenched with saturated aqueous ammonium chloride solution and extracted with ethyl acetate three times. The combined organic phases were washed with saturated aqueous sodium chloride solution, dried over sodium sulfate and filtrated. The resultant



Scheme 3 Reagents and conditions: (a) LDA, *p*NsCl, tetrahydrofuran (THF), –78 to 0 °C, 81%; (b) LiOH, THF-H_2O, room tempertature (rt), 76%; (c) DEAD, Ph_3P, benzene, 0 °C, 66%; (d) $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C to rt, 69%.



Scheme 4 Reagents and conditions: (a) tetra-*n*-butylammonium fluoride (TBAF), tetrahydrofuran (THF), room temperature (rt), 84%; (b) Bu_3SnH, $(Ph_3P)_2PdCl_2$, THF, rt, 62%; (c) DEAD, Ph_3P, benzene, 0 °C, 91%; (d) $HSCH_2CO_2H$, DBU, MeCN, rt; (e) formalin, AcOH, $NaBH_3CN$, MeOH, rt, quant. (two steps); (f) Na/naphthalene, THF, –78 to 0 °C; (g) $(PhSeO)_2O$, indole, THF, 45 °C, 59% (two steps); (h) Boc_2O, DMAP, MeCN, rt, 67%; (i) NIS, trifluoroacetic acid (TFA), THF, –10 °C; (j) CO (1 atm); $Pd(PPh_3)_4$, Et_3N, DMF-MeOH, 75 °C; (k) TFA, Me_2S, CH_2Cl_2, 40 °C; (l) pyridine, MeCN, 50 °C, 42% (four steps); (m) NaOH, EtOH-H_2O, 35 °C, 36%.

filtrate was concentrated *in vacuo* and the resultant residue was purified with flash column chromatography on silica gel (10–50% ethyl acetate in hexane) to give an *N*-acyloxazolidinone (34.15 g, 78%) as a pale yellow oil. $[\alpha]_D^{22.3}$ –45.2 (*c* 1.01, $CHCl_3$); IR (film) 1778, 1702, 1391, 1364, 1198, 1051, 1027, 748, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.2 Hz, 1H), 7.37–7.17 (m, 8H), 4.70 (m, 1H), 4.49 (d, *J* = 18.3 Hz, 1H), 4.37 (d, *J* = 18.3 Hz, 1H), 4.29–4.21 (m, 2H), 3.35 (d, *J* = 13.6 Hz, 1H), 2.80 (dd, *J* = 13.6, 10.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9 (C), 153.5 (C), 135.1 (C), 134.0 (C), 132.7 (CH), 131.8 (CH), 129.4 (CH), 129.0 (CH), 128.9 (CH), 127.5 (CH), 127.3 (CH), 125.3 (C), 66.4 (CH_2), 55.4 (CH), 43.1 (CH_2), 37.8 (CH_2), HR-MS (ESI) 396.0247 (calcd for $C_{18}H_{16}BrNNaO_3$ 396.0211). To a solution of the *N*-acyloxazolidinone (12.33 g, 32.94 mmol) in toluene (75 ml) and tetrahydrofuran (150 ml) was added sodium hexamethyldisilazide (0.6 M in toluene, 72.0 ml, 42.8 mmol) at –78 °C. The reaction mixture was stirred at –78 °C for 1 h and then allyl bromide (13.92 ml, 164.5 mmol) was added. After stirring at ambient temperature for 4 h, the reaction mixture was quenched with saturated aqueous ammonium chloride solution and extracted with ethyl acetate three times. The combined organic phases were washed with saturated aqueous sodium chloride solution, dried over sodium sulfate and filtrated. The resultant filtrate was concentrated *in vacuo* and the resultant residue was purified with flash column chromatography on silica gel (5–35% ethyl acetate in hexane) to give the title compound **7** (10.09 g, 74%, dr = 13.6:1) as a pale yellow oil. The diastereomer ratio was determined based on the ^1H NMR, and the mixture was used for the next reaction without separation. $[\alpha]_D^{22.4}$ –83.8 (*c* 1.08, $CHCl_3$); IR (film) 1781, 1697, 1385, 1208, 1051, 1023, 750, 701 cm^{-1}; major isomer: ^1H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.2 Hz, 1H), 7.37–7.22 (m, 7H), 7.12 (dd, *J* = 8.2, 7.8 Hz, 1H), 5.92 (m, 1H), 5.52 (dd, *J* = 8.7, 6.4 Hz, 1H), 5.18 (d, *J* = 17.4 Hz, 1H), 5.08 (d, *J* = 10.5 Hz, 1H), 4.68 (dddd, *J* = 10.1, 7.3, 3.7, 3.2 Hz, 1H), 4.15–4.09 (m, 2H), 3.33 (dd, *J* = 13.3, 3.2 Hz, 1H), 2.84 (m, 1H), 2.77 (dd, *J* = 13.3, 10.1 Hz, 1H), 2.61 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7 (C), 152.6 (C), 137.7 (C), 135.2 (C), 134.9 (CH), 133.2 (CH), 129.4 (CH), 128.9 (CH), 128.7 (CH), 128.6 (CH), 127.5 (CH), 127.3 (CH), 125.3 (C), 117.5 (CH_2), 65.9 (CH_2), 55.8 (CH), 48.4 (CH), 37.9 (CH_2), 36.8 (CH_2), HR-MS (ESI) 436.0563 (calcd for $C_{21}H_{20}BrNNaO_3$ 436.0524).

(*R*)-2-(2-bromophenyl)pent-4-en-1-ol (8)

To a suspension of lithium aluminum hydride (2.64 g, 69.6 mmol) in tetrahydrofuran (200 ml) was added a solution of **7** (19.2 g, 46.4 mmol) in tetrahydrofuran (200 ml) at 0 °C using a dropping funnel. After stirring at 0 °C for 30 min, the reaction mixture was diluted with tetrahydrofuran (400 ml). To the reaction mixture were added water (2.64 ml), 15% aqueous sodium hydroxide (2.64 ml) and water (7.92 ml) at 0 °C successively. After stirring at room temperature for 40 min, the reaction mixture was then filtered through a Celite pad and the filter cake was washed with ethyl acetate. The resulting filtrate was concentrated *in vacuo* and the resultant residue was purified with flash column chromatography on silica gel (10–45% ethyl acetate in hexane) to give the title compound **8** (9.49 g, 85%) as a colorless oil. $[\alpha]_D^{22.6}$ +2.15 (*c* 1.02, $CHCl_3$); IR (film) 1470, 1437, 1051, 1023, 752 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.0 Hz, 1H), 7.29 (dd, *J* = 7.5, 6.9 Hz, 1H), 7.25 (d, *J* = 6.9 Hz, 1H), 7.08 (dd, *J* = 8.0, 7.5 Hz, 1H), 5.74 (m, 1H), 5.04 (d, *J* = 16.9 Hz, 1H), 4.98 (d, *J* = 10.4 Hz, 1H), 3.79 (d, *J* = 6.3 Hz, 2H), 3.51 (dddd, *J* = 13.1, 6.9, 6.3, 6.3 Hz, 1H), 2.53 (ddd, *J* = 14.4, 6.9, 6.3 Hz, 1H), 2.42 (ddd, *J* = 14.4, 13.1, 6.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.8 (C), 135.8 (CH), 133.0 (CH), 128.2 (CH), 127.9 (CH), 127.4 (CH), 125.6 (C), 116.6 (CH_2), 65.3 (CH_2), 45.7 (CH), 35.7 (CH_2), HR-MS (direct analysis on real time) 241.0243 (calcd for $C_{11}H_{14}BrO$ 241.0228).

(*R*)-*N*-(2-(2-bromophenyl)pent-4-en-1-yl)-4-methylbenzenesulfonamide (9)

To a solution of alcohol **8** (9.49 g, 39.3 mmol), *N*-(*t*-Boc)-*p*-toluenesulfonamide (12.8 g, 47.1 mmol) and triphenylphosphine (12.4 g, 47.1 mmol) in toluene (200 ml) and tetrahydrofuran (50 ml) was added diisopropyl azodicarboxylate (ca. 1.9 M in toluene, 25 ml, 48 mmol) at room temperature. After stirring at 80 °C for 2 h, the reaction mixture was cooled to room temperature, quenched with saturated aqueous sodium chloride solution and extracted with ethyl acetate three times. The combined organic phases were dried over sodium sulfate and filtrated. The filtrate was concentrated *in vacuo* and the resultant residue was purified with flash column chromatography on neutral silica gel (10–30% ethyl acetate in hexane) to give an *N*-Boc tosylamide (19.2 g, 99%) as a brown oil. $[\alpha]_D^{23.1}$ $[\alpha]_D$ +12.7 (*c* 1.05, $CHCl_3$); IR (film) 1729, 1353, 1285, 1155, 1087, 674 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.2 Hz, 1H), 7.43 (d, *J* = 8.2 Hz, 2H), 7.38 (d, *J* = 7.8 Hz, 1H), 7.33 (dd, *J* = 8.2, 7.8 Hz, 1H), 7.17 (d, *J* = 8.2 Hz, 2H), 7.10 (dd, *J* = 8.2, 8.2 Hz, 1H), 5.67 (dddd, *J* = 17.4,

10.5, 6.9, 4.6 Hz, 1H), 4.99 (d, J=17.4 Hz, 1H), 4.94 (d, J=10.5 Hz, 1H), 4.18 (dd, J=14.6, 9.2 Hz, 1H), 4.03 (dd, J=14.6, 6.0 Hz, 1H), 3.93 (m, 1H), 2.54–2.39 (m, 2H), 2.38 (s, 3H), 1.31 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9 (C), 150.9 (C), 143.8 (CH), 140.8 (C), 137.2 (C), 135.2 (CH), 132.8 (CH), 128.9 (CH), 128.1 (CH), 127.7 (CH), 127.5 (CH), 127.3 (C), 116.8 (CH_2), 84.2 (C), 74.3 (CH), 50.5 (CH_2), 37.6 (CH_2), 27.8 (CH_3), 21.5 (CH_3), HR-MS (ESI) 516.0867 (calcd for $C_{23}H_{28}BrNO_4S$ 516.0820). To a solution of the *N*-Boc tosylamide (19.2 g, 38.8 mmol) in dichloromethane (200 ml) was added TFA (100 ml) at room temperature. After stirring for 1 h, the reaction mixture was concentrated *in vacuo*. The excess TFA was removed azeotropically with toluene, giving the title compound **9** (15.1 g) as a brown oil, which was used in the next reaction without purification. $[\alpha]_D^{23.4}$ –6.07° (*c* 1.13, $CHCl_3$); IR (film) 3273, 1683, 1437, 1327, 1159, 1088, 813, 754, 667 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J=8.2 Hz, 2H), 7.49 (d, J=8.7 Hz, 1H), 7.25 (d, J=8.2 Hz, 2H), 7.21 (dd, J=8.7, 7.8 Hz, 1H), 7.06–7.03 (m, 2H), 5.60 (dddd, J=17.4, 9.2, 6.8, 4.1 Hz, 1H), 4.95 (d, J=17.4 Hz, 1H), 4.94 (d, J=9.2 Hz, 1H), 4.63 (t, J=5.0 Hz, 1H), 3.41 (dddd, J=7.3, 7.3, 6.9, 6.9 Hz, 1H), 3.21 (ddd, J=13.3, 6.9, 6.4 Hz, 1H), 3.15 (ddd, J=13.3, 7.3, 6.0 Hz, 1H), 2.40–2.30 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.2 (C), 139.8 (C), 136.6 (C), 134.7 (CH), 133.1 (CH), 129.6 (CH), 128.2 (CH), 127.8 (CH), 127.7 (CH), 126.9 (CH), 125.3 (C), 117.3 (CH_2), 46.2 (CH_2), 42.9 (CH), 36.7 (CH_2), 21.4 (CH_3), HR-MS (ESI) 416.0276 (calcd for $C_{18}H_{20}BrNNaO_2S$ 416.0295).

(*R*)-3-allyl-1-tosylindoline (10)

To a solution of tosylamide **9** (15.1 g, < 38.8 mmol) in dimethyl sulfoxide (300 ml) were added copper iodide (12.0 g, 58.2 mmol) and cesium acetate (25.0 g, 116 mmol) and the reaction mixture was degassed with three freeze–thaw cycles. After stirring at room temperature overnight, the mixture was quenched with saturated ammonium chloride solution and extracted with ethyl acetate three times. The combined organic phases were washed with saturated aqueous sodium chloride solution, dried over sodium sulfate and filtrated. The resultant filtrate was concentrated *in vacuo* and the resultant residue was purified with flash column chromatography on neutral silica gel (5–12.5% ethyl acetate in hexane) to give the title compound **10** (7.12 g, 58% in two steps) as a brown oil. $[\alpha]_D^{23.2}$ –9.78 (*c* 1.11, $CHCl_3$); IR (film) 1597, 1477, 1459, 1354, 1167, 1090, 1048, 754, 665 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73–7.69 (m, 3H), 7.31–7.24 (m, 3H), 7.13 (d, J=7.5 Hz, 1H), 7.03 (dd, J=7.5, 7.4 Hz, 1H), 5.68 (dddd, J=17.3, 9.8, 7.5, 6.3 Hz, 1H), 5.06 (d, J=9.8 Hz, 1H), 5.01 (d, J=17.3 Hz, 1H), 4.01 (dd, J=10.9, 6.9 Hz, 1H), 3.66 (dd, J=10.9, 6.3 Hz, 1H), 3.26 (dddd, J=8.0, 6.9, 6.3, 5.1 Hz, 1H), 2.41 (s, 3H), 2.34 (m, 1H), 2.00 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.0 (C), 141.7 (C), 134.8 (CH), 134.7 (C), 133.9 (C), 129.5 (CH), 128.0 (CH), 127.2 (CH), 124.4 (CH), 123.5 (CH), 117.4 (CH_2), 114.8 (CH), 54.7 (CH_2), 39.2 (CH), 39.0 (CH_2), 21.5 (CH_3), HR-MS (ESI) 336.1021 (calcd for $C_{18}H_{19}NNaO_2S$ 336.1034).

(*R*)-3-(1-tosylindolin-3-yl)propanoic acid (11)

To a solution of 2-methyl-2-butene (27.54 ml, 259.2 mmol) in tetrahydrofuran (200 ml) was added borane tetrahydrofuran complex solution (1.0 M in tetrahydrofuran, 129.6 ml, 129.6 mmol) at 0 °C. After stirring at 0 °C for 30 min, a solution of indoline **10** (13.55 g, 43.20 mmol) in tetrahydrofuran (200 ml) was added at 0 °C using a dropping funnel. After stirring at 0 °C for 1 h, 15% aqueous sodium hydroxide (142 ml, 518 mmol) and aqueous hydrogen peroxide (30 wt%, 71.0 g, 518 mmol) were added successively at 0 °C. After stirring at 0 °C for 20 min, saturated aqueous sodium thiosulfate (200 ml) was added at 0 °C and the solution was partitioned between ethyl acetate three times. The combined organic phases were washed with saturated aqueous sodium chloride solution, dried over sodium sulfate and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (20–80% ethyl acetate in hexane) to give an alcohol (13.87 g, 97%) as a colorless oil. $[\alpha]_D^{23.5}$ –13.7 (*c* 1.00, $CHCl_3$); IR (film) 1597, 1477, 1458, 1351, 1166, 1089, 1051, 754, 665 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, J=8.0 Hz, 2H), 7.63 (d, J=8.0 Hz, 1H), 7.25–7.18 (m, 3H), 7.06 (d, J=7.4 Hz, 1H), 6.97 (dd, J=7.4, 7.4 Hz, 1H), 3.99 (dd, J=10.3, 9.3 Hz, 1H), 3.59–3.55 (m, 3H), 3.12 (dddd, J=10.3, 9.3, 8.5, 5.1 Hz, 1H), 2.36 (s, 3H), 1.64 (m, 1H), 1.52–1.46 (m, 2H), 1.37 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.0 (C), 141.6 (C), 135.2 (C), 133.8 (C), 129.6 (CH), 128.0 (CH), 127.2 (CH), 124.3 (CH), 123.6 (CH), 114.7 (CH), 62.5 (CH_2), 55.4 (CH_2), 39.7 (CH), 30.9 (CH_2), 29.7 (CH_2), 21.4 (CH_3), HR-MS (ESI) 354.1135 (calcd for $C_{18}H_{21}NNaO_3S$ 354.1139). To a solution of the alcohol (13.87 g, 41.84 mmol) in acetone (300 ml) was added Jones reagent (2.5 M, 42 ml, 104.5 mmol) at 0 °C. After stirring at 0 °C for 1 h, isopropyl alcohol (9.58 ml, 125 mmol) was added. After stirring at room temperature for 30 min, the reaction mixture was then filtered through a Celite pad and the filter cake was washed with acetone. The resulting filtrate was concentrated *in vacuo* and the resultant residue was purified with flash column chromatography on silica gel (20–100% ethyl acetate in hexane) to give the title compound **11** (11.10 g, 77%) as an off-white solid, melting point: 115–118 °C (decomp.). $[\alpha]_D^{24.1}$ –19.5 (*c* 1.01, $CHCl_3$); IR (film) 3028, 2927, 1707, 1597, 1477, 1458, 1352, 1166 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67–7.62 (m, 3H), 7.26–7.19 (m, 3H), 7.07 (d, J=7.3 Hz, 1H), 6.99 (dd, J=7.8, 7.3 Hz, 1H), 3.96 (dd, J=10.6, 9.2 Hz, 1H), 3.58 (dd, J=10.6, 5.5 Hz, 1H), 3.17 (dddd, J=9.2, 7.8, 5.5, 5.5 Hz, 1H), 2.35 (s, 3H), 2.25 (t, J=7.8 Hz, 2H), 1.85 (dtd, J=13.3, 7.8, 5.5 Hz, 1H), 1.57 (dtd, J=13.3, 7.8, 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.7 (C), 144.2 (C), 141.6 (C), 134.1 (C), 133.6 (C), 129.6 (CH), 128.3 (CH), 127.2 (CH), 124.5 (CH), 123.7 (CH), 114.8 (CH), 55.0 (CH_2), 38.9 (CH), 30.8 (CH_2), 29.3 (CH_2), 21.4 (CH_3).

(*R*)-4-benzyl-3-(3-((*R*)-1-tosylindolin-3-yl)propanoyl)oxazolidin-2-one (12)

To a solution of indoline-3-propionic acid **11** (11.10 g, 32.13 mmol) in tetrahydrofuran (150 ml) were added triethylamine (4.92 ml, 35.3 mmol) and pivaloyl chloride (4.14 ml, 33.7 mmol) at 0 °C. After forming white suspension, the reaction mixture was cooled to –78 °C. In the other reaction flask, *n*-butyllithium (2.66 M in hexane, 14.5 ml, 38.5 mmol) was added to a solution of (*R*)-4-benzyl-2-oxazolidinone (**6**, 6.83 g, 38.5 mmol) in tetrahydrofuran (150 ml) at –78 °C and then the reaction mixture was allowed to warm up to 0 °C, which was added to the white suspended solution via cannular for 20 min at –78 °C. After stirring at room temperature for 3 h, the reaction mixture was quenched with saturated aqueous ammonium chloride solution and extracted with ethyl acetate three times. The combined organic phases were washed with saturated aqueous sodium chloride solution, dried over sodium sulfate and filtrated. The resultant filtrate was concentrated *in vacuo* and the resultant residue was purified with flash column chromatography on silica gel (20–70% ethyl acetate in hexane) to give the title compound **12** (16.24 g, 100%) as a pale yellow oil. $[\alpha]_D^{23.5}$ –40.8 (*c* 1.02, $CHCl_3$); IR (film) 3027, 2923, 1779, 1698, 1477, 1388, 1352, 1166, 754 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J=8.2 Hz, 2H), 7.63 (d, J=8.2 Hz, 1H), 7.33–7.16 (m, 8H), 7.11 (d, J=7.3 Hz, 1H), 6.98 (dd, J=7.3, 7.3 Hz, 1H), 4.63 (dddd, J=9.6, 9.6, 9.2, 3.7 Hz, 1H), 4.18 (dd, J=10.1, 9.6 Hz, 1H), 4.18 (dd, J=10.1, 9.2 Hz, 1H), 3.99 (dd, J=10.6, 9.2 Hz, 1H), 3.60 (dd, J=10.6, 6.0 Hz, 1H), 3.24 (dd, J=13.8, 3.7 Hz, 1H), 3.18 (m, 1H), 2.98–2.82 (m, 2H), 2.74 (dd, J=13.8, 9.6 Hz, 1H), 2.34 (s, 3H), 1.96 (m, 1H), 1.59 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1 (C), 153.3 (C), 144.1 (C), 141.6 (C), 135.0 (C), 134.5 (C), 133.6 (C), 129.6 (CH), 129.3 (CH), 128.9 (CH), 128.2 (CH), 127.3 (CH), 127.2 (CH), 124.5 (CH), 123.6 (CH), 114.7 (CH), 66.2 (CH_2), 55.3 (CH_2), 55.0 (CH), 39.2 (CH), 37.8 (CH_2), 33.0 (CH_2), 29.0 (CH_2), 21.4 (CH_3), HR-MS (ESI) 527.1613 (calcd for $C_{28}H_{28}N_2NaO_5S$ 527.1616).

(*R*)-4-benzyl-3-((2*R*,3*R*)-6-((*tert*-butyldiphenylsilyl)oxy)-3-hydroxy-2-(((*R*)-1-tosylindolin-3-yl)methyl)hex-4-ynoyl)oxazolidin-2-one (14)

To a solution of *N*-acyloxazolidinone **12** (16.24 g, 32.13 mmol) in dichloromethane (150 ml) were added titanium chloride (1.0 M in dichloromethane, 35.3 ml, 35.3 mmol) and *N,N*-diisopropylethylamine (13.9 ml, 80.2 mmol) at –78 °C, which formed dark purple solution. After stirring at –78 °C for 40 min, hexamethylphosphoric triamide (8.42 ml, 48.1 mmol) and aldehyde **13** (12.5 g, 38.5 mmol) in dichloromethane (100 ml) were successively added to the reaction mixture and then the resulting mixture was allowed to warm up to room temperature. After stirring for 1 h, the reaction mixture was quenched with saturated aqueous ammonium chloride solution and extracted with dichloromethane three times. The combined organic phases were washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution successively. Then, the organic layers were dried over sodium

sulfate and filtrated. The resultant filtrate was concentrated *in vacuo* and the resultant residue was purified with flash column chromatography on silica gel (5–25% ethyl acetate in hexane) to give the title compound **14** (16.73 g, 63%) as a brown oil. The stereochemistry of the product was deduced based on the typical selectivity of the asymmetric reaction. The *syn* relationship of the aldol product was determined by NOE after conversion into an oxazolidinone. $[\alpha]_D^{23.5}$ –24.5 (*c* 0.970, $CHCl_3$); IR (film) 3497, 2930, 2857, 1779, 1696, 1598, 1478, 1389, 1352, 1167, 1109, 760 cm^{-1}; major isomer; ^1H NMR (500 MHz, $CDCl_3$) δ 7.70–7.64 (m, 7H), 7.40–7.33 (m, 6H), 7.29 (d, *J*=7.5 Hz, 2H), 7.22 (dd, *J*=8.0, 7.5 Hz, 1H), 7.19–7.16 (m, 5H), 7.12 (d, *J*=7.5 Hz, 1H), 6.99 (dd, *J*=7.5, 7.5 Hz, 1H), 4.65 (m, 1H), 4.50 (br s, 1H), 4.37–4.30 (m, 2H), 4.20 (m, 1H), 4.12–4.08 (m, 2H), 4.03 (dd, *J*=10.9, 9.1 Hz, 1H), 3.62 (dd, *J*=10.9, 6.3 Hz, 1H), 3.23 (dd, *J*=13.1, 3.5 Hz, 1H), 3.07 (m, 1H), 2.73 (dd, *J*=13.1, 9.8 Hz, 1H), 2.30 (s, 3H), 2.24 (ddd, *J*=13.8, 10.3, 4.0 Hz, 1H), 2.19 (d, *J*=4.5 Hz, 1H), 1.63 (ddd, *J*=13.8, 6.9, 4.0 Hz, 1H), 1.02 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5 (C), 153.3 (C), 143.9 (C), 141.5 (C), 135.5 (CH), 135.4 (CH), 134.9 (C), 134.8 (C), 133.7 (C), 132.8 (C), 132.7 (C), 129.8 (CH), 129.5 (CH), 129.2 (CH), 128.9 (CH), 128.2 (CH), 127.7 (CH), 127.7 (CH), 127.4 (CH), 127.3 (CH), 124.5 (CH), 123.7 (CH), 114.7 (CH), 85.1 (C), 82.7 (C), 66.2 (CH_2), 63.6 (CH), 55.7 (CH_2), 55.6 (CH), 52.4 (CH_2), 46.7 (CH), 38.0 (CH_2), 38.0 (CH), 33.5 (CH_2), 26.6 (CH_3), 21.4 (CH_3), 19.0 (C), HR-MS (ESI) 849.3028 (calcd for $C_{48}H_{50}N_2NaO_7SSi$ 849.3005).

(4*R*,5*S*)-5-(3-((*tert*-butyldiphenylsilyl)oxy)prop-1-yn-1-yl)-4-(((*R*)-1-tosylindolin-3-yl)methyl)oxazolidin-2-one (15)

To a solution of aldol adduct **14** (16.73 g, 20.22 mmol) in tetrahydrofuran (200 ml) was added hydrazine anhydrous (4.52 ml, 151 mmol) at room temperature. After stirring for 2 h, the reaction mixture was quenched with 1 N hydrochloric acid solution and extracted with ethyl acetate three times. The combined organic phases were dried over sodium sulfate and filtrated. The resultant filtrate was concentrated *in vacuo* and the resultant residue was used for the next step without further purification. To a solution of the residue in dichloromethane (200 ml) were added *t*-butyl nitrite (2.90 ml, 24.2 mmol) and boron trifluoride diethyl ether complex (3.00 ml, 24.2 mmol) at 0 °C. After stirring at 0 °C for 30 min, the reaction mixture was quenched with saturated aqueous sodium bicarbonate solution and extracted with dichloromethane three times. The combined organic phases were dried over sodium sulfate and filtrated. The filtrate was concentrated *in vacuo* and the resultant residue was filtered through flash column chromatography on neutral silica gel (10–45% ethyl acetate in hexane) to remove (*R*)-4-benzyl-2-oxazolidinone. The combined organic phases were concentrated *in vacuo* and the resultant residue was used in the next reaction without further purification. The residue was dissolved with toluene (200 ml) and then the reaction mixture was heated at 110 °C for 50 min. The reaction mixture was concentrated *in vacuo* and the resultant residue was purified with flash column chromatography on silica gel (20–70% ethyl acetate in hexane) to give the title compound **15** (8.50 g, 63% in three steps) as a yellow oil. $[\alpha]_D^{22.8}$ –4.43 (*c* 1.01, $CHCl_3$); IR (film) 2930, 2857, 1757, 1476, 1355, 1167, 1110, 1090, 754 cm^{-1}; major isomer; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71–7.61 (m, 7H), 7.40–7.30 (m, 6H), 7.22–7.18 (m, 3H), 7.10 (br s, 1H), 6.99 (d, *J*=7.3 Hz, 1H), 6.92 (dd, *J*=7.8, 7.3 Hz, 1H), 5.21 (d, *J*=8.2 Hz, 1H), 4.31 (s, 2H), 4.00 (dd, *J*=10.1, 9.6 Hz, 1H), 3.86 (ddd, *J*=10.1, 8.2, 4.6 Hz, 1H), 3.61 (dd, *J*=10.1, 5.0 Hz, 1H), 3.24 (m, 1H), 2.32 (s, 3H), 1.91 (ddd, *J*=14.2, 5.5, 4.6 Hz, 1H), 1.58 (ddd, *J*=14.2, 10.1, 3.7 Hz, 1H), 0.99 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6 (C), 144.3 (C), 141.3 (C), 135.4 (CH), 134.1 (C), 133.3 (C), 132.5 (C), 129.9 (CH), 129.7 (CH), 128.3 (CH), 127.7 (CH), 127.3 (CH), 124.4 (CH), 123.9 (CH), 114.7 (CH), 89.4 (C), 76.8 (C), 70.0 (CH), 54.8 (CH_2), 52.5 (CH), 52.3 (CH_2), 36.9 (CH_2), 36.4 (CH), 26.5 (CH_3), 21.4 (CH_3), 19.0 (C), HR-MS (ESI) 687.2316 (calcd for $C_{38}H_{40}N_2NaO_5SSi$ 687.2342).

(4*R*,5*S*)-5-(3-((*tert*-butyldiphenylsilyl)oxy)prop-1-yn-1-yl)-3-((4-nitrophenyl)sulfonyl)-4-(((*R*)-1-tosylindolin-3-yl)methyl) oxazolidin-2-one (16)

To a solution of oxazolidinone **15** (8.50 g, 12.7 mmol) in tetrahydrofuran (100 ml) was added lithium diisopropylamide (0.870 M in hexane and tetrahydrofuran, 32.2 ml, 28.1 mmol) at –78 °C. After stirring at –78 °C for 20 min, 4-nitrobenzenesulfonyl chloride (6.23 g, 28.1 mmol) in tetrahydrofuran (30 ml) was added to the reaction mixture. After stirring at 0 °C for 30 min, the reaction mixture was quenched with saturated aqueous ammonium chloride solution and extracted with ethyl acetate three times. The combined organic phases were washed with saturated aqueous sodium chloride solution and dried over sodium sulfate and filtrated. The resultant filtrate was concentrated *in vacuo* and the resultant residue was purified with flash column chromatography on neural silica gel (5–50% ethyl acetate in hexane) to give the title compound **16** (8.83 g, 81%) as a yellow oil. $[\alpha]_D^{23.4}$ –10.1 (*c* 1.10, $CHCl_3$); IR (film) 2931, 2857, 1787, 1534, 1349, 1169, 1107, 1090 cm^{-1}; major isomer; ^1H NMR (500 MHz, $CDCl_3$) δ 8.39 (d, *J*=9.2 Hz, 2H), 8.22 (d, *J*=9.2 Hz, 2H), 7.71 (d, *J*=8.0 Hz, 2H), 7.66 (d, *J*=8.0 Hz, 1H), 7.62–7.60 (m, 4H), 7.42–7.40 (m, 2H), 7.36–7.32 (m, 4H), 7.27–7.22 (m, 3H), 7.05 (d, *J*=7.5 Hz, 1H), 6.98 (dd, *J*=7.5, 7.1 Hz, 1H), 5.06 (d, *J*=7.5 Hz, 1H), 4.51 (ddd, *J*=8.6, 8.0, 7.5 Hz, 1H), 4.32 (s, 2H), 4.02 (dd, *J*=10.9, 9.1 Hz, 1H), 3.75 (dd, *J*=10.9, 5.1 Hz, 1H), 3.39 (dddd, *J*=9.1, 8.6, 5.1, 4.6 Hz, 1H), 2.34 (s, 3H), 2.21–2.08 (m, 2H), 0.98 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.1 (C), 150.4 (C), 144.3 (C), 142.4 (C), 141.5 (C), 135.4 (CH), 135.4 (CH), 134.4 (C), 133.3 (C), 132.3 (C), 130.0 (CH), 129.7 (CH), 128.6 (CH), 127.8 (CH), 127.3 (CH), 124.6 (CH), 124.5 (CH), 123.9 (CH), 114.8 (CH), 92.0 (C), 74.8 (C), 69.9 (CH), 58.3 (CH), 55.3 (CH_2), 52.2 (CH_2), 36.4 (CH_2), 36.3 (CH), 26.4 (CH_3), 21.4 (CH_3), 19.0 (C), HR-MS (ESI) 872.2101 (calcd for $C_{44}H_{43}N_3NaO_9S_2Si$ 872.2107).

N-((2*R*,3*S*)-6-((*tert*-butyldiphenylsilyl)oxy)-3-hydroxy-1-((*R*)-1-tosylindolin-3-yl)hex-4-yn-2-yl)-4-nitrobenzenesulfonamide (17)

To a solution of *N*-*p*-nitrobenzenesulfonyl-oxazolidinone **16** (8.83 g, 10.3 mmol) in tetrahydrofuran (100 ml) and water (50 ml) was added lithium hydroxide (746 mg, 31.1 mmol) at room temperature. After stirring for 1 h, the reaction mixture was quenched with saturated aqueous ammonium chloride solution and extracted with ethyl acetate three times. The combined organic phases were dried over sodium sulfate and filtrated. The resultant filtrate was concentrated *in vacuo* and the resultant residue was purified with flash column chromatography on neutral silica gel (20–70% ethyl acetate in hexane) to give the title compound **17** (6.54 g, 76%) as a bright yellow oil. $[\alpha]_D^{23.7}$ + 13.1 (*c* 1.12, $CHCl_3$); IR (film) 2931, 2857, 1531, 1348, 1164, 1109, 1090, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J*=8.2 Hz, 2H), 8.01 (d, *J*=8.2 Hz, 2H), 7.68–7.59 (m, 7H), 7.42–7.31 (m, 6H), 7.23–7.18 (m, 3H), 6.99–6.95 (m, 2H), 5.01 (d, *J*=9.6 Hz, 1H), 4.30 (s, 2H), 4.07 (br s, 1H), 3.89 (dd, *J*=11.0, 9.6 Hz, 1H), 3.60 (dd, *J*=11.0, 5.5 Hz, 1H), 3.46 (m, 1H), 3.27 (m, 1H), 2.35 (s, 3H), 1.75 (br s, 1H), 1.60 (ddd, *J*=14.2, 11.4, 3.2 Hz, 1H), 1.39 (ddd, *J*=14.2, 8.2, 3.2 Hz, 1H), 1.01 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.9 (C), 146.4 (C), 144.3 (C), 141.5 (C), 135.5 (CH), 135.4 (CH), 134.6 (C), 133.5 (C), 132.8 (C), 132.7 (C), 130.0 (CH), 130.0 (CH), 129.7 (CH), 128.3 (CH), 128.2 (CH), 127.7 (CH), 127.7 (CH), 127.3 (CH), 124.2 (CH), 124.1 (CH), 123.8 (CH), 115.0 (CH), 86.9 (C), 81.0 (C), 64.5 (CH), 56.3 (CH), 55.0 (CH_2), 52.3 (CH_2), 36.3 (CH_2), 36.2 (CH), 26.5 (CH_3), 21.5 (CH_3), 19.0 (C), HR-MS (ESI) 846.2345 (calcd for $C_{43}H_{45}N_3NaO_8S_2Si$ 846.2315).

(*R*)-3-(((2*R*,3*R*)-3-(3-((*tert*-butyldiphenylsilyl)oxy)prop-1-yn-1-yl)-1-((4-nitrophenyl)sulfonyl)aziridin-2-yl)methyl)-1-tosylindoline (18)

To a solution of amino alcohol **17** (6.52 g, 7.91 mmol) and triphenylphosphine (2.49 g, 9.49 mmol) in benzene (50 ml) was added diethyl azodicarboxylate (2.2 M in toluene, 4.3 ml, 9.5 mmol) at 0 °C. After stirring at 0 °C for 20 min, the reaction mixture was quenched with saturated aqueous sodium chloride solution and extracted with ethyl acetate three times. The combined organic phases were dried over sodium sulfate and filtrated. The resultant filtrate was concentrated *in vacuo* and the resultant residue was purified with flash column chromatography on neutral silica gel (5–20% ethyl acetate in hexane) to give the title compound **18** (4.22 g, 66%) as a yellow oil. $[\alpha]_D^{23.9}$ –31.2 (*c* 1.14, $CHCl_3$); IR (film) 2931, 2857, 1599, 1533, 1476, 1349, 1309, 1167, 1109, 1089 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.32 (d, *J*=9.1 Hz, 2H), 8.14 (d, *J*=8.7 Hz, 2H), 7.70–7.69 (m, 6H), 7.65 (d, *J*=8.0 Hz, 1H), 7.45–7.38 (m, 6H), 7.26–7.20 (m, 3H), 7.02 (d, *J*=7.5 Hz, 1H), 6.98 (dd, *J*=7.5, 7.5 Hz, 1H), 4.35 (s, 2H), 3.95 (dd, *J*=10.9, 9.1 Hz, 1H), 3.67 (dd, *J*=10.9, 5.1 Hz, 1H), 3.22 (dddd, *J*=10.9, 10.3, 5.1, 4.0 Hz, 1H), 3.05–3.00 (m, 2H), 2.37 (s, 3H), 1.83 (ddd, *J*=14.3, 7.1, 4.0 Hz, 1H), 1.66 (ddd, *J*=14.2, 10.3, 5.8 Hz, 1H),

1.02 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.5 (C), 144.3 (C), 144.3 (C), 141.4 (C), 135.5 (CH), 135.5 (CH), 133.6 (C), 133.4 (C), 132.6 (C), 129.9 (CH), 129.7 (CH), 129.2 (CH), 128.6 (CH), 127.8 (CH), 127.8 (CH), 127.3 (CH), 124.2 (CH), 124.2 (CH), 123.8 (CH), 114.9 (CH), 85.4 (C), 76.7 (C), 54.5 (CH_2), 52.6 (CH_2), 46.3 (CH), 38.0 (CH), 36.4 (CH), 35.3 (CH_2), 26.6 (CH_3), 21.5 (CH_3), 19.1 (C), HR-MS (ESI) 828.2201 (calcd for $C_{43}H_{43}N_3NaO_7S_2Si$ 828.2209).

N-((2a*R*,4*R*,5*R*)-5-(3-((*tert*-butyldiphenylsilyl)oxy)prop-1-yn-1-yl)-1-tosyl-1,2,2a,3,4,5-hexahydrobenzo[*cd*]indol-4-yl)-4-nitrobenzenesulfonamide (19)

To a solution of aziridine **18** (4.22 g, 5.23 mmol) in dichloromethane (40 ml) was added boron trifluoride diethyl ether complex (1.42 ml, 11.5 mmol) at 0 °C. After stirring at room temperature for 30 min, the reaction mixture was quenched with saturated aqueous sodium bicarbonate solution and extracted with dichloromethane three times. The combined organic phases were dried over sodium sulfate and filtrated. The filtrate was concentrated *in vacuo* and the resultant residue was purified with flash column chromatography on neutral silica gel (10–50% ethyl acetate in hexane) to give the title compound **19** (2.93 g, 69%) as a yellow oil. $[\alpha]_D^{23.6}$ –79.7 (*c* 1.00, $CHCl_3$); IR (film) 3273, 2930, 2857, 1595, 1531, 1449, 1349, 1165, 1088, 739, 703 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, *J*=8.5 Hz, 2H), 8.01 (d, *J*=8.5 Hz, 2H), 7.70 (d, *J*=8.0 Hz, 2H), 7.58 (d, *J*=7.5 Hz, 4H), 7.39–7.24 (m, 9H), 7.08 (dd, *J*=8.0, 8.0 Hz, 1H), 6.77 (d, *J*=8.0 Hz, 1H), 5.35 (m, 1H), 4.23 (dd, *J*=11.5, 11.5 Hz, 1H), 4.17 (s, 2H), 3.75 (m, 1H), 3.54 (m, 1H), 3.21 (m, 1H), 3.14 (dd, *J*=11.5, 9.1 Hz, 1H), 2.34 (s, 3H), 2.04 (m, 1H), 1.60 (m, 1H), 1.01 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.0 (C), 146.0 (C), 144.5 (C), 140.4 (C), 135.4 (CH), 133.4 (C), 132.9 (C), 132.8 (C), 130.7 (C), 129.9 (CH), 129.8 (CH), 129.8 (CH), 129.5 (C), 129.0 (CH), 128.3 (CH), 127.6 (CH), 127.6 (CH), 127.3 (CH), 124.4 (CH), 122.9 (CH), 112.4 (CH), 83.6 (C), 82.6 (C), 57.9 (CH_2), 54.4 (CH), 52.6 (CH_2), 35.2 (CH), 31.4 (CH), 29.3 (CH_2), 26.5 (CH_3), 21.5 (CH_3), 19.0 (C), HR-MS (ESI) 828.2202 (calcd for $C_{43}H_{43}N_3NaO_7S_2Si$ 828.2209).

N-((2a*R*,4*R*,5*R*)-5-((*E*)-3-hydroxy-2-(tributylstannyl)prop-1-en-1-yl)-1-tosyl-1,2,2a,3,4,5-hexahydrobenzo[*cd*]indol-4-yl)-4-nitrobenzenesulfonamide (20)

To a solution of tricyclic compound **19** (2.93 g, 3.63 mmol) in tetrahydrofuran (20 ml) was added tetra-*n*-butylammonium fluoride (1.0 M in tetrahydrofuran, 18.1 ml, 18.1 mmol) at room temperature. After stirring for 1 h, the reaction mixture was quenched with saturated aqueous ammonium chloride solution and extracted with ethyl acetate three times. The combined organic phases were dried over sodium sulfate and filtrated. The resultant filtrate was concentrated *in vacuo* and the resultant residue was purified with flash column chromatography on neutral silica gel (10–70% ethyl acetate in hexane) to give a propargyl alcohol (1.73 g, 84%) as a yellow oil. $[\alpha]_D^{24.2}$ –74.2 (*c* 1.17, $CHCl_3$); IR (film) 2920, 1599, 1530, 1450, 1349, 1309, 1163, 1092 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 8.33 (d, *J*=8.6 Hz, 2H), 8.05 (d, *J*=8.6 Hz, 2H), 7.65 (d, *J*=8.6 Hz, 2H), 7.28 (d, *J*=8.0 Hz, 1H), 7.23 (d, *J*=8.6 Hz, 2H), 7.10 (dd, *J*=8.0, 7.5 Hz, 1H), 6.87 (d, *J*=7.5 Hz, 1H), 4.20 (dd, *J*=6.9, 6.9 Hz, 1H), 3.91 (s, 2H), 3.75 (dd, *J*=4.6, 3.5 Hz, 1H), 3.57 (s, 1H), 3.20–3.14 (m, 2H), 2.28 (s, 3H), 2.02 (ddd, *J*=13.0, 4.6, 4.6 Hz, 1H), 1.57 (ddd, *J*=13.0, 11.5, 3.5 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 151.3 (C), 148.0 (C), 145.9 (C), 141.8 (C), 134.7 (C), 133.0 (C), 132.0 (C), 130.9 (CH), 129.7 (CH), 129.3 (CH), 128.5 (CH), 125.4 (CH), 124.2 (CH), 113.8 (CH), 84.9 (C), 83.4 (C), 59.2 (CH_2), 55.8 (CH), 50.6 (CH_2), 36.0 (CH), 32.7 (CH), 30.8 (CH_2), 21.5 (CH_3), HR-MS (ESI) 590.1044 (calcd for $C_{27}H_{25}N_3NaO_7S_2$ 590.1031). To a solution of the propargyl alcohol (1.73 g, 3.04 mmol) and bis(triphenylphosphine)palladium (II) dichloride (428 mg, 0.608 mmol) in tetrahydrofuran (25 ml) was added tri-*n*-butyltin hydride (0.965 ml, 3.64 mmol) at room temperature. After stirring for 1 h, the reaction mixture was quenched with saturated aqueous sodium chloride solution and extracted with ethyl acetate three times. The combined organic phases were dried over sodium sulfate and filtrated. The resultant filtrate was concentrated *in vacuo* and the resultant residue was purified with flash column chromatography on silica gel (0–30% ethyl acetate in hexane) to give the title compound **20** (1.62 g, 62%) as a yellow oil. $[\alpha]_D^{21.8}$ –74.6 (*c* 0.982, $CHCl_3$); IR (film) 2954, 2923, 2869, 1598, 1531, 1449, 1348, 1307, 1163, 1092 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (d, *J*=8.6 Hz, 2H), 8.01 (d, *J*=8.6 Hz, 2H), 7.69 (d, *J*=8.6 Hz, 2H), 7.30 (d, *J*=8.0 Hz, 1H), 7.26 (d, *J*=8.6 Hz, 2H), 7.06 (dd, *J*=8.0, 8.0 Hz, 1H), 6.56 (d, *J*=8.0 Hz, 1H), 5.70 (d, *J*=6.3 Hz, 1H), 5.12 (d, *J*=9.2 Hz, 1H), 4.29–4.21 (m, 3H), 3.61 (dd, *J*=9.2, 4.1 Hz, 1H), 3.44 (dddd, *J*=6.3, 4.9, 4.3, 4.1 Hz, 1H), 3.25–3.13 (m, 2H), 2.39 (s, 3H), 2.08 (ddd, *J*=12.6, 4.9, 4.6 Hz, 1H), 1.84 (s, 1H), 1.63 (m, 1H), 1.49–1.34 (m, 6H), 1.27–1.19 (m, 6H), 0.88–0.75 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.9 (C), 148.3 (C), 146.4 (C), 144.3 (C), 140.4 (C), 138.7 (CH), 134.2 (C), 133.6 (C), 130.3 (C), 129.8 (CH), 128.8 (CH), 128.2 (CH), 127.3 (CH), 124.3 (CH), 122.4 (CH), 112.1 (CH), 63.0 (CH_2), 57.9 (CH_2), 54.4 (CH), 43.1 (CH), 31.6 (CH_2), 30.6 (CH), 29.0 (CH_2), 27.2 (CH_2), 21.5 (CH_3), 13.6 (CH_3), 10.0 (CH_2), HR-MS (ESI) 882.2225 (calcd for $C_{39}H_{53}N_3NaO_7S_2Sn$ 882.2244).

(5a*R*,6a*R*,10a*R*)-7-((4-nitrophenyl)sulfonyl)-4-tosyl-9-(tributylstannyl)-4,5,5a,6,6a,7,8,10a-octahydroindolo[4,3-*fg*]quinoline (21)

To a solution of allyl alcohol **20** (1.62 g, 1.88 mmol) and triphenylphosphine (594 mg, 2.26 mmol) in benzene (20 ml) was added diethyl azodicarboxylate (2.2 M in toluene, 1.0 ml, 2.2 mmol) at 0 °C. After stirring at 0 °C for 30 min, the reaction mixture was quenched with saturated aqueous sodium chloride solution and extracted with ethyl acetate three times. The combined organic phases were dried over sodium sulfate and filtrated. The resultant filtrate was concentrated *in vacuo* and the resultant residue was purified with flash column chromatography on neutral silica gel (5–15% ethyl acetate in hexane) to give the title compound **21** (1.45 g, 91%) as a yellow oil. $[\alpha]_D^{21.4}$ –79.4 (*c* 1.28, $CHCl_3$); IR (film) 2954, 2924, 2851, 1597, 1530, 1453, 1349, 1162, 1094 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J*=8.7 Hz, 2H), 7.95 (d, *J*=8.7 Hz, 2H), 7.68 (d, *J*=8.3 Hz, 2H), 7.44 (d, *J*=8.2 Hz, 1H), 7.24 (d, *J*=8.3 Hz, 2H), 7.21 (dd, *J*=8.2, 7.8 Hz, 1H), 6.91 (d, *J*=7.8 Hz, 1H), 6.42 (s, 1H), 4.38–4.31 (m, 2H), 3.91 (d, *J*=17.9 Hz, 1H), 3.39 (d, *J*=10.5 Hz, 1H), 3.34–3.24 (m, 2H), 3.15 (ddd, *J*=10.5, 10.1, 9.2 Hz, 1H), 2.61 (ddd, *J*=13.9, 10.1, 7.1 Hz, 1H), 2.38 (s, 3H), 1.78 (ddd, *J*=13.9, 9.2, 5.5 Hz, 1H), 1.52–1.44 (m, 6H), 1.36–1.27 (m, 6H), 0.96–0.80 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.7 (C), 147.6 (C), 144.2 (C), 141.3 (C), 140.4 (C), 136.0 (C), 135.0 (CH), 133.8 (C), 131.2 (C), 129.7 (CH), 128.3 (CH), 128.1 (CH), 127.2 (CH), 124.2 (CH), 117.9 (CH), 112.8 (CH), 59.4 (CH), 58.7 (CH_2), 52.6 (CH_2), 40.0 (CH), 32.7 (CH), 30.4 (CH_2), 29.0 (CH_2), 27.3 (CH_2), 21.5 (CH_3), 13.6 (CH_3), 9.42 (CH_2), HR-MS (ESI) 882.2141 (calcd for $C_{39}H_{51}N_3NaO_6S_2Sn$ 864.2138).

(5a*R*,6a*R*,10a*R*)-7-methyl-4-tosyl-9-(tributylstannyl)-4,5,5a,6,6a,7,8,10a-octahydroindolo[4,3-*fg*]quinoline (22)

To a solution of tetracyclic compound **21** (1.45 g, 1.72 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (2.56 ml, 17.2 mmol) in acetonitrile (25 ml) was added thioglycolic acid (794 mg, 8.62 mmol) at room temperature. After stirring at room temperature for 45 min, the reaction mixture was quenched with saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate three times. The combined organic phases were dried over sodium sulfate and filtrated. The filtrate was concentrated *in vacuo* and the resultant residue was used in the next reaction without further purification. To a solution of the residue, formalin (2.0 ml) and acetic acid (2.0 ml) in methanol (17.5 ml) was added sodium cyanoborohydride (1.08 g, 17.2 mmol) at room temperature. After stirring at room temperature for 1 h, the reaction mixture was quenched with saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate three times. The combined organic phases were washed with saturated aqueous sodium chloride solution, dried over sodium sulfate and filtrated. The filtrate was concentrated *in vacuo* and the resultant residue was purified with flash column chromatography on silica gel (1–3% methanol in chloroform) to give the title compound **22** (1.35 g, including thioglycolic acid) as a yellow oil. $[\alpha]_D^{22.8}$ –122.1 (*c* 1.11, $CHCl_3$); IR (film) 2954, 2924, 2868, 2850, 1595, 1453, 1356, 1166, 1094 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, *J*=7.5 Hz, 2H), 7.40 (d, *J*=8.0 Hz, 1H), 7.23 (d, *J*=7.5 Hz, 2H), 7.17 (dd, *J*=8.0, 7.5 Hz, 1H), 6.87 (d, *J*=7.5 Hz, 1H), 6.32 (s, 1H), 4.38 (m, 1H), 3.40 (d, *J*=16.6 Hz, 1H), 3.31–3.22 (m, 2H), 3.18 (m, 1H), 2.91 (m, 1H), 2.36 (s, 3H), 2.28 (s, 3H), 2.03–1.96 (m, 2H), 1.69 (m, 1H), 1.52–1.46 (m, 6H),

1.34–1.27 (m, 6H), 0.93–0.83 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.8 (C), 139.9 (C), 139.5 (C), 137.6 (C), 133.6 (C), 132.3 (CH), 131.2 (C), 129.5 (CH), 127.8 (CH), 127.0 (CH), 118.7 (C, thioglycolic acid), 117.7 (CH), 112.2 (CH), 62.5 (CH), 61.2 (CH_2), 59.4 (CH_2), 47.9 (CH_2, thioglycolic acid), 40.4 (CH), 40.4 (CH_3), 31.9 (CH), 29.8 (CH_2), 28.8 (CH_2), 27.1 (CH_2), 21.2 (CH_3), 13.3 (CH_3), 8.91 (CH_2), HR-MS (ESI) 671.2682 (calcd for $C_{34}H_{51}N_2O_2SSn$ 671.2693).

(6a*R*,10a*R*)-*tert*-butyl 7-methyl-9-(tributylstannyl)-6,6a,7,8-tetrahydroindolo[4,3-*fg*]quinoline-4(10a*H*)-carboxylate (23)

To a solution of tertiary amine **22** (1.35 g, <1.72 mmol) in tetrahydrofuran (14 ml) was added sodium naphthalenide (1.00 M in tetrahydrofuran, 8.60 ml, 8.60 mmol) at −78 °C and then the reaction mixture was allowed to warm up to 0 °C. After stirring at 0 °C for 1 h, the reaction mixture was quenched with saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate three times. The combined organic phases were washed with saturated aqueous sodium chloride solution, dried over sodium sulfate and filtrated. The filtrate was concentrated *in vacuo* and the resultant residue was used in the next reaction without further purification. To a solution of the residue and indole (665 mg, 5.67 mmol) in tetrahydrofuran (17 ml) was added benzeneseleninic acid anhydride (681 mg, 1.89 mmol) at room temperature. After stirring at 45 °C for 1 h, the reaction mixture was quenched with saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate three times. The combined organic phases were dried over sodium sulfate and filtrated. The filtrate was concentrated *in vacuo* and the resultant residue was purified with flash column chromatography on neutral silica gel (10–100% ethyl acetate in hexane and then 10% methanol in ethyl acetate) to give an indole (521 mg, 59% in two steps) as a brown oil, which was contaminated with impurities. $[\alpha]_D^{23.6}$ −117.8 (*c* 0.985, $CHCl_3$); IR (film) 2954, 2924, 2869, 2848, 2360, 2339, 1597, 1454, 1375, 1349 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (br s, 1H), 7.73 (d, 0.25H, impurity), 7.19–7.18 (m, 2H), 7.04 (d, *J*=4.5 Hz, 1H), 6.86 (s, 1H), 6.61 (s, 1H), 3.91 (d, *J*=9.1 Hz, 1H), 3.61 (d, *J*=17.4 Hz, 1H), 3.36 (dd, *J*=14.2, 2.8 Hz, 1H), 3.23 (d, *J*=17.4 Hz, 1H), 2.86 (dd, *J*=14.2, 12.4 Hz, 1H), 2.73 (m, 1H), 2.56 (s, 3H), 2.36 (m, 0.84H, impurity), 1.65–1.53 (m, 6H), 1.42–1.30 (m, 6H), 1.09–0.92 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0 (C), 133.9 (CH), 133.5 (C), 131.9 (C), 129.6 (C, impurity), 126.2 (C), 122.6 (CH), 118.0 (CH), 112.4 (CH), 111.5 (C), 108.6 (CH), 63.5 (CH), 62.1 (CH_2), 41.9 (CH), 40.2 (CH_3), 29.0 (CH_2), 27.3 (CH_2), 26.4 (CH_2), 13.6 (CH_3), 9.00 (CH_2), HR-MS (ESI) 515.2444 (calcd for $C_{27}H_{43}N_2Sn$ 515.2448). To a solution of the indole (521 mg, 1.01 mmol) and *N*,*N*-dimethyl-4-aminopyridine (12.4 mg, 0.101 mmol) in acetonitrile (10 ml) was added di-*t*-butyl dicarbonate (288 mg, 1.31 mmol) at room temperature. After stirring for 1 h, the solvent was removed under reduced pressure. The resultant residue was purified with flash column chromatography on neutral silica gel (5–15% ethyl acetate in hexane) to give the title compound **23** (414 mg, 67%) as a brown oil. $[\alpha]_D^{22.0}$ −75.8 (*c* 0.981, $CHCl_3$); IR (film) 2954, 2924, 2851, 2765, 1730, 1438, 1391, 1359, 1298, 1283, 1155 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (br s, 1H), 7.31–7.28 (m, 2H), 7.17 (d, *J*=7.5 Hz, 1H), 6.52 (br s, 1H), 3.75 (m, 1H), 3.54 (d, *J*=16.6 Hz, 1H), 3.27 (dd, *J*=14.4, 3.5 Hz, 1H), 3.12 (d, *J*=16.6 Hz, 1H), 2.69 (dd, *J*=14.4, 9.5 Hz, 1H), 2.54 (ddd, *J*=9.5, 6.3, 3.5 Hz, 1H), 2.47 (s, 3H), 1.66 (s, 9H), 1.55–1.47 (m, 6H), 1.39–1.26 (m, 6H), 1.04-0.86 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.0 (C), 139.0 (C), 133.2 (CH), 132.6 (C), 128.6 (2C, overlapped), 124.9 (CH), 119.2 (CH), 116.8 (C), 116.3 (CH), 112.7 (CH), 83.0 (C), 63.2 (CH), 62.3 (CH_2), 42.0 (CH), 40.6 (CH_3), 29.0 (CH_2), 28.0 (CH_3), 27.3 (CH_2), 26.4 (CH_2), 13.7 (CH_3), 8.99 (CH_2), HR-MS (ESI) 615.2990 (calcd for $C_{32}H_{51}N_2O_2Sn$ 615.2972).

(6a*R*,10a*R*)-*tert*-butyl 9-iodo-7-methyl-6,6a,7,8-tetrahydroindolo[4,3-*fg*]quinoline-4(10a*H*)-carboxylate (24)

To a solution of indole derivative **23** (408 mg, 0.665 mmol) in tetrahydrofuran (6.5 ml) was added TFA (61.5 ml, 0.798 mmol) and *N*-iodosuccinimide (180 mg, 0.798 mmol) at −10 °C. After stirring for 20 min, the reaction mixture was quenched with saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate three times. The combined organic phases were dried over sodium sulfate and filtrated. The filtrate was concentrated *in vacuo* and the resultant residue was purified with flash column chromatography on neutral silica gel (10–20% ethyl acetate in hexane) to give the title compound **24** (271 mg, including impurities) as a brown oil. $[\alpha]_D^{21.6}$ −151.7 (*c* 0.81, $CHCl_3$); IR (film) 2975, 2926, 2849, 1729, 1437, 1391, 1354, 1297, 1283, 1257, 1156 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (br s, 1H), 7.30–7.26 (m, 2H), 7.09 (d, *J*=7.8 Hz, 1H), 7.02 (s, 1H), 3.79 (m, 1H), 3.56 (d, *J*=16.7 Hz, 1H), 3.40 (d, *J*=16.7 Hz, 1H), 3.12 (d, *J*=11.9 Hz, 1H), 2.77 (dd, *J*=12.8, 11.9 Hz, 1H), 2.72 (dd, *J*=13.7, 12.8 Hz, 1H), 2.49 (s, 3H), 1.68 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.8 (C), 134.5 (CH), 133.2 (C), 130.7 (C), 128.2 (C), 125.0 (CH), 119.4 (CH), 116.5 (CH), 116.2 (C), 113.2 (CH), 94.8 (C), 83.3 (C), 66.1 (CH_2), 61.2 (CH), 42.3 (CH), 38.5 (CH_3), 28.1 (CH_3), 27.8 (CH_2, Bu_3SnX), 26.7 (CH_2, Bu_3SnX), 26.2 (CH_2), 17.4 (CH_2, Bu_3SnX), 13.5 (CH_3, Bu_3SnX), HR-MS (ESI) 451.0889 (calcd for $C_{20}H_{24}IN_2O_2$ 451.0882).

(6a*R*)-4-*tert*-butyl 9-methyl 7-methyl-6a,7,8,9-tetrahydroindolo[4,3-*fg*]quinoline-4,9(6*H*)-dicarboxylate (25)

To a solution of alkenyl iodide **24** (270 mg, including impurities) and triethylamine (0.251 ml, 1.80 mmol) in *N*,*N*-dimethylformamide (3.0 ml) and methanol (3.0 ml) was added tetrakis(triphenylphosphine)palladium(0) (139 mg, 0.120 mmol) at room temperature. The reaction system was substituted with the atmospheric carbon monoxide and then heated at 75 °C for 1 h. The reaction mixture was cooled to room temperature and quenched with saturated aqueous sodium chloride solution and extracted with diethyl ether three times. The combined organic phases were dried over sodium sulfate and filtrated. The resultant filtrate was concentrated *in vacuo* and the resultant residue was purified with flash column chromatography on neutral silica gel (5–40% ethyl acetate in hexane) to give the title compound **25** (118 mg, dr=1.8:1, including triphenylphosphine) as a brown oil. IR (film) 2954, 2852, 2798, 1729, 1442, 1393, 1057, 910, 854 cm^{-1}; HR-MS (ESI) 405.1797 (calcd for $C_{22}H_{26}N_2NaO_4$ 405.1790). Major isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (br s, 1H), 7.33 (m, 1H), 7.27–7.24 (m, 2H), 6.57 (s, 1H), 3.74 (s, 3H), 3.69 (m, 1H), 3.41 (dd, *J*=10.9, 4.0 Hz, 1H), 3.25 (m, 1H), 3.06 (m, 1H), 2.68–2.58 (m, 2H), 2.54 (s, 3H), 1.63 (s, 9H). Minor isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (br s, 1H), 7.33 (m, 1H), 7.27–7.24 (m, 2H), 6.52 (s, 1H), 3.70 (s, 3H), 3.34–3.30 (m, 2H), 3.25 (m, 1H), 3.06 (m, 1H), 2.68–2.58 (m, 1H), 2.51 (s, 3H), 2.51 (m, 1H), 1.63 (s, 9H).

(+)-Lysergic acid (1)

To a solution of a mixture of β,γ-unsaturated ester **25** (6.5 mg of the above material was used) in dichloromethane (0.15 ml) and dimethyl sulfide (0.15 ml) was added TFA (0.60 ml) at room temperature. After stirring for 1 h at 40 °C, the reaction mixture was diluted with toluene (1 ml). The solvents were removed under reduced pressure and the resultant residue was used in the next reaction without any purification. To a solution of the residue in acetonitrile (0.15 ml) was added pyridine (0.30 ml) at room temperature. After stirring at 50 °C for 20 min, the solvent was removed under reduced pressure and the resultant residue was purified with thin layer column chromatography on silica gel (7.5% methanol in chloroform) to give a diastereomeric mixture of methyl esters (4.3 mg, 42% in four steps, dr=1.8:1) as a brown oil. IR (film) 2950, 2850, 2799, 1732, 1558, 1540, 1507, 1455, 1435, 1068, 1057, 749 cm^{-1}; HR-MS (ESI) 283.1460 (calcd for $C_{17}H_{19}N_2O_2$ 283.1446). Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (br s, 1H), 7.24–7.16 (m, 3H), 6.92 (s, 1H), 6.60 (s, 1H), 3.78 (s, 3H), 3.72 (m, 1H), 3.53 (dd, *J*=15.1, 5.5 Hz, 1H), 3.31 (m, 1H), 3.20 (m, 1H), 2.78–2.69 (m, 2H), 2.62 (s, 3H). Minor isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (br s, 1H), 7.24–7.16 (m, 3H), 6.90 (s, 1H), 6.56 (d, *J*=4.1 Hz, 1H), 3.72 (s, 3H), 3.43 (dd, *J*=14.8, 5.2 Hz, 1H), 3.36 (dd, *J*=11.4, 3.7 Hz, 1H), 3.31 (m, 1H), 3.20 (m, 1H), 2.78–2.69 (m, 2H), 2.57 (s, 3H). The ^{1}H NMR spectrum was in good accordance with those reported by Ohno and co-workers.[20] To solution of the mixture of methyl esters (8.3 mg, 0.0293 mmol) in ethanol (0.30 ml) was added 1 N aqueous sodium hydroxide (0.30 ml). The reaction mixture was stirred at 35 °C for 2 h. One normal of hydrochloric acid solution was used to carefully adjust the pH to 6 and stirred at 0 °C for 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**, 2.8 mg, 36%) as a pale red-brown solid. $[\alpha]_D^{20.9}$ +46.1 (*c* 0.14, pyridine); lit.[16] $[\alpha]_D^{20}$ +40 (*c* 0.50, pyridine); IR (film) 3243, 3207, 2921, 2850, 1597, 1455, 1375 cm^{-1}; ^{1}H NMR (400 MHz, C_5D_5N) δ 11.71 (br s, 1H), 7.45 (d, *J*=7.8 Hz, 1H), 7.43

(d, J=7.8 Hz, 1H), 7.30 (dd, J=7.8, 7.8 Hz, 1H), 7.21–7.19 (m, 2H), 4.06 (m, 1H), 3.64 (dd, J=14.6, 5.5 Hz, 1H), 3.54 (dd, J=14.6, 5.0 Hz, 1H), 3.29 (m, 1H), 2.96–2.88 (m, 2H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, C_5D_5N) δ 175.1 (C), 136.7 (C), 135.9 (C), 128.9 (C), 127.3 (C), 123.3 (CH), 120.1 (CH), 119.8 (CH), 112.2 (CH), 110.5 (C), 110.5 (CH), 63.8 (CH), 56.0 (CH_2), 43.9 (CH_3), 43.3 (CH), 27.9 (CH_2), HR-MS (ESI) 291.1111 (calcd for $C_{16}H_{16}N_2NaO_2$ 291.1109).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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