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PII: S0040-4020(18)30433-2

DOI: 10.1016/j.tet.2018.04.044

Reference: TET 29459

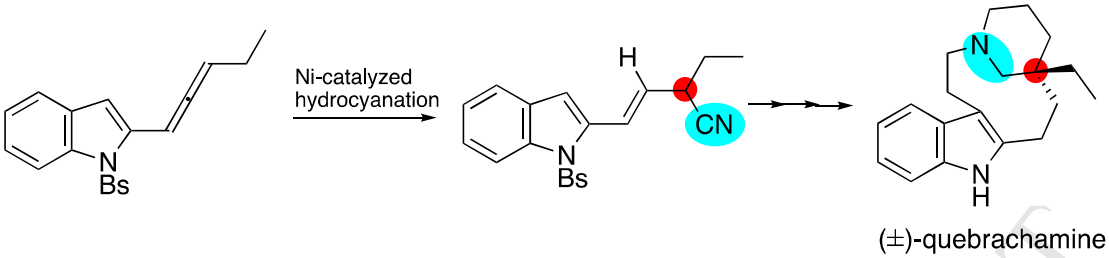
To appear in: *Tetrahedron*

Received Date: 23 March 2018

Revised Date: 13 April 2018

Accepted Date: 16 April 2018

Please cite this article as: Matsumoto K, Arai S, Nishida A, Formal synthesis of (±) —quebrachamine through regio- and stereoselective hydrocyanation of arylallene, *Tetrahedron* (2018), doi: 10.1016/ j.tet.2018.04.044.



(±)-quebrachamine

Formal synthesis of (±) —quebrachamine through regio- and stereoselective hydrocyanation of arylallene

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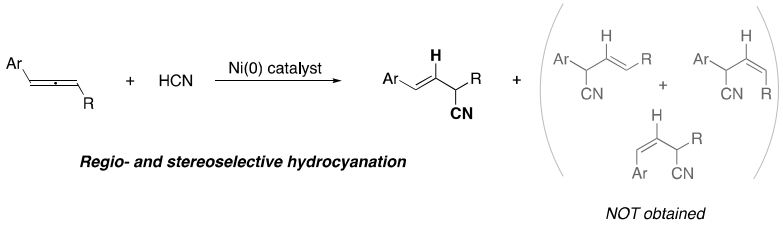
[**Abstract**] This article describes the formal synthesis of quebrachamine based on regio- and stereoselective hydrocyanation of 1,3-disubstituted allenes. Allenyl C-C double bonds are effectively discriminated through Ni-catalyzed hydrocyanation and a CN group is utilized as a synthon of piperidine ring. Several steps from HCN adduct afforded known intermediates to quebrachamine.

Keywords: Alkaloid; Allene; Hydrocyanation; Nickel catalysis; Quebrachamine.

1. Introduction

A cyano group is a key element or precursor for the synthesis of nitrogen heterocycles or biologically important molecules.[1] Therefore, its facile introduction to organic molecules, particularly to non-activated C-C multiple bonds under metal catalysis, has been major challenge in synthetic chemistry. One of the most reliable and well-investigated cyanation protocols is Ni-catalyzed hydrocyanation, which allows to use various C-C multiple bonds such as alkenes,[2-4] alkynes,[5] conjugated dienes[6] and allenes.[7] Based on these background, we established new protocols of hydrocyanative transformations such as cyclization,[8] cross coupling reaction,[9] cyclopropane cleavage[10] and chirality transfer[11] using allenyl substrates. Through these investigation, we realized that the aromatic substituents in 1,3-disubstituted allenes are key to determine the regio- and stereoselectivity of the hydrocyanation adducts (Scheme 1).[10a] This reaction selectively installs C-H and C-CN bonds to give *trans*-olefin that conjugates aromatic rings, and these observation prompted us to realize their synthetic utility. In this article, we report a formal synthesis of biologically important molecule using above regio- and stereoselective hydrocyanation of allenes as a key step.

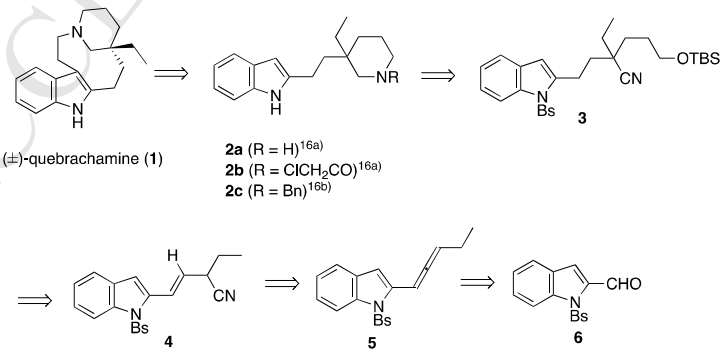


Scheme 1. Ni-catalyzed hydrocyanation of arylallenes

Quebrachamine (**1**) has been isolated from Aspidosperma quebracho tree bark over a centry ago.[12] Its intriguing tetracyclic core involving indole and nine-membered heterocycle as well as biological activity such as α-adrenergic blocking behavior in urogenital tissue[13] have been attractive features as a synthetic target and more than 60 synthetic examples[14] have been reported to date since the Stork's first total synthesis in 1963.[15]

2. Results and discussion

Retrosynthetic analysis of **1** is outlined in Scheme 2. A cyano group would be a key synthon for construction of piperidine ring in known intermediates (**2a-c**).[16] Their precursor (**3**) is a carbonitrile involving a quaternary carbon, which could be constructed by α-alkylation of **4** and regioselective hydrocyanation of allenylindole (**5**) would give **4** as a single isomer. Finally, a known formylindole derivative (**6**) is set as a starting material.

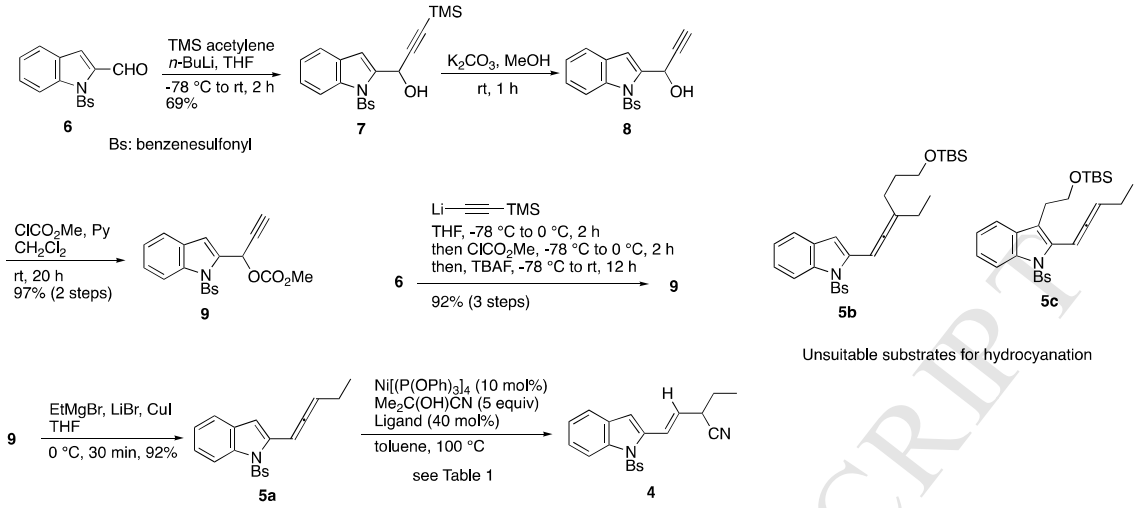


Scheme 2. Retrosynthetic analysis of **1**

Initially, **6** was subjected to alkynylation using Li trimethylsilyl acetylide to give the corresponding alcohol (**7**). After removal of a TMS group to **8**, sequential acylation using $ClCO_2Me$ gave **9** in 97% (2 steps). This 3-step reaction can be modified to increase practicality, step-economy and operational simplicity. The one-pot procedure is as follows; the first step is the addition of Li-acetylide to **6**, the second step is acylation of resulting alkoxide intermediate with $ClCO_2Me$ and the third step is the removal of a TMS group using TBAF to give **8** in 92% yield (3 steps). Next Cu-mediated alkylation using EtMgBr with LiBr gave the allenylindole (**5a**) in 92% yield (Scheme 3).

The substrate in hand, we next investigated Ni-catalyzed hydrocyanation of **5a**. As described in Table 1, this reaction was completed within 30 min under thermal conditions and sensitive in the external phosphorous ligand, for example, PAr_3 or $MePPh_2$ gave **4** in the range of 25-34% yield (entries 1-3) and PCy_3 resulted in slower reaction (entry 4). On the other hand, 2-$PyPPh_2$ improved the yield of **4** to 53% (entry 5). A bidentate phosphine such as dppb (20 mol%) did not work well to improve the yield of **4** (entry 6). This reaction did not give any isolable regio- and stereoisomers of **4** however its yield was difficult to increase even after ligand optimization. One of the reason would be the higher reactivity of **4** with Ni(0) species to cause decomposition or polymerization triggered by metalacycle formation.

This hydrocyanation reaction was quite sensitive for the steric environment around allenyl double bonds. When tri-substituted allene such as **5b** was subjected to similar conditions, the reaction efficacy dramatically decreased to give any desired product with recovery of **5b** in 18% yield even after 11 h. 3-Substituted indole **5c** was also inert to give the trace amount of the desired HCN adduct, unfortunately.[17]



Scheme 3. Synthetic transformation to **4**

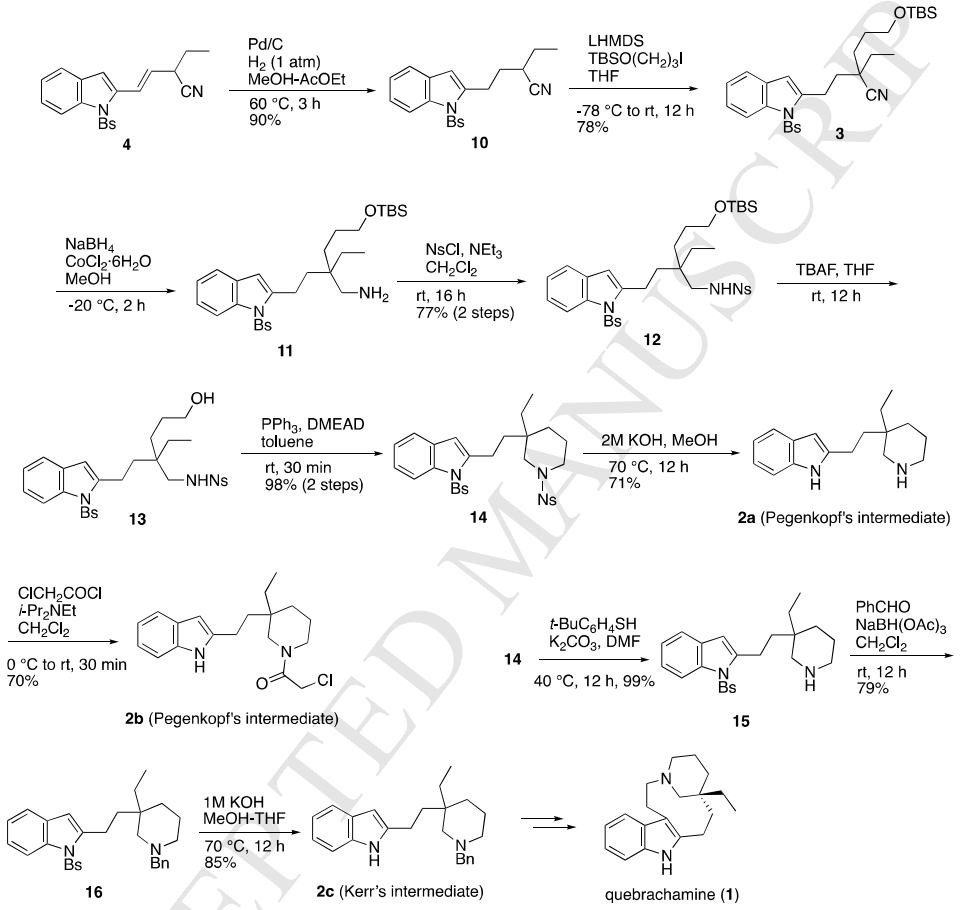
Entry	Ligand	Time (min)	Yield of **4** (%)
1	PPh_3	30	31
2	P(4-MeOPh)$_3$	30	25
3	$MePPh_2$	20	34
4	PCy_3	60	34
5	2-$PyPPh_2$	20	53
6	$Ph_2P(CH_2)_4PPh_2$*	20	20

*20 mol% was used.

Table 1. Ni-catalyzed hydrocyanation of **5a**

Next task is piperidine formation utilizing a CN group in **4** as an aminomethyl group. Initially, hydrogenation of **4** was employed to give **10** in 90% yield, and then the α-alkylation to construct the quaternary carbon successfully proceeded to give **3** in 78% yield. This 2-step protocol was found to be reasonable because the alkylation of **4** with LHMDS gave a complex mixture with lower conversion of the desired alkylated product. Sequential reduction of **3** to the corresponding primary amine (**11**) followed by nosylation gave **12** in 78% (2 steps). After removal of a TBS group with TBAF, Mitsunobu cyclization of **13** gave the piperidine (**14**) in 98% yield (2 steps). Sulfonyl functionalities in **14** were then removed under basic media to give **2a** as a known intermediate for (±)-quebrachamine, however its NMR spectra did not show good agreement to the reported value.[16a] So piperidine **2a**

was next transformed to **2b** and its structure was fully characterlized to be Pagenkopf's intermediate.[16a] The removal of a Ns group in **14** gave **15**, which was converted to **16** by reductive amination. Final deprotection of a Bs group gave Kerr's intermediate (**2c**), which was identified by NMR spectra.[16b] The syntheses of above two known intermediates (**2b,c**) indicates the completion of the formal synthesis of (±)-quebrachamine (**1**).



Scheme 4. Synthesis of **2**

3. Conclusion

In summary, our protocol of hydrocyanation using arylallenes is key technology to control the regio- and stereoselectivity in the products, which could be applied to formal synthesis of (±)-quebrachamine (**1**). These results prove the synthetic utility of Ni-catalyzed regio- and stereoselective hydrocyanation and the further investigation is currently undergoing.

4. Experimental

4.1 General

All reactions were performed with dry solvents under argon atmosphere and the reagents were purified by the standard methods. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm Merck silica gel plates (60F-254). Column chromatography was performed with silica gel (Fuji Silysia, PSQ-60B) or NH-silica (Fuji Silysia, DM2035). NMR spectra were recorded on spectrometers of JEOL JMN-ECS-400, ECP-400, ECZ-400, ECZ-600, and ECA-600 operating at 400 or 600 MHz for ^{1}H NMR and 100 or 150 MHz for ^{13}C NMR with calibration using residual undeuterated solvent as an internal reference. IR spetra were recorded on JASCO FT/IR-4700. High resolution mass spectra were measured by The AccuTOFLC-plus JMS-T100LP (Ionization method: ESI).

4.2.1. Methyl (1-(1-(phenylsulfonyl)-1H-indol-2-yl)prop-2-yn-1-yl) carbonate (**9**)

To a solution of trimethylsilyl acetylene (521.2 mg, 5.31 mmol, 1.2 equiv.) in THF (78.4 mL), *n*-butyl lithium (1.55 M in *n*-hexane, 3.7 mL, 5.75 mmol, 1.3 equiv.) was added dropwise at –78 °C. A solution of **6** (1.26 g, 4.42 mmol) in THF (10 mL) was then added slowly and the reaction mixture was stirred at –78 °C for 1 h and 0 °C for 1 h. After cooling at –78 °C, methyl chloroformate (0.68 mL, 8.84 mmol, 2.0 equiv.) was added slowly to above reaction mixture. Then the resulting mixture was stirred at –78 °C for 1 h and 0 °C for 1 h respectively. Finally, tetrabutylammonium fluoride (1.0 M in THF, 8.84 mL, 8.84 mmol, 2.0 equiv.) was added at –78 °C and the reaction mixture was allowed to be warmed to room temperature gradually with stirring for 1 h. The reaction was quenched by the addition of sat. NH_4Cl (80 mL) at 0 °C and the resulting mixture was stirred for 12 h. The separated aqueous layer was extracted with AcOEt (40 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in *vacuo*. The crude residue was purified by flash column chromatography (*n*-hexane:AcOEt = 8:1) to give **9** (1.50 g, 4.07 mmol) in 92% yield as a colorless solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.76 (d, *J* = 2.4 Hz, 1H), 3.88 (s, 3H), 6.99 (d, *J* = 2.4 Hz, 1H), 7.22 (s, 1H), 7.25 (dd, *J* = 7.2 Hz, 1H), 7.35 (dd, *J* = 7.2, 7.2 Hz, 1H), 7.43 (dd, *J* = 7.6, 8.0 Hz, 2H), 7.52-7.55 (m, 2H), 7.88 (d, *J* = 7.6 Hz, 2H), 8.05 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ:

55.3, 62.6, 75.9, 78.2, 114.5, 114.6, 121.7, 123.9, 125.9, 126.7, 128.1, 129.1, 133.9, 134.2, 137.3, 138.1, 154.3; IR (ATR) ν: 3297, 2955, 2124, 1749, 1446, 1375, 1255, 1174, 639 cm^{-1}; HRMS (ESI) *m/z*: calcd for $C_{19}H_{15}NNaO_5S$ $[M+Na]^+$ 392.0569, found 392.0573; mp: 102-103 °C.

4.2.2. 2-(Penta-1,2-dien-1-yl)-1-(phenylsulfonyl)-1H-indole (**5a**)

To a solution of flame dried LiBr (1.18 g, 13.6 mmol, 6.0 equiv.) and CuI (1.29 g, 6.80 mmol, 3.0 equiv.) in THF (34 mL), EtMgBr (3.0 M in Et_2O, 2.27 mL, 6.80 mmol, 3.0 equiv.) was added at 0 °C. After being stirred for 30 min, the solution of **9** (836.8 mg, 2.27 mmol) in THF (14 mL) was added to the reaction mixture at 0 °C. After being stirred at the same temperature for 30 min, the reaction was quenched by the addition of sat. NH_4Cl (50 mL). The aqueous layer was extracted with Et_2O (30 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in *vacuo*. The crude residue was purified by flash column chromatography (*n*-hexane:Et_2O = 20:1) to give **5a** (677.2 mg, 2.09 mmol) in 92% yield as a pale yellow oil. *Note: **5a** should be used immediately without storage because of its unstability.* ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.06 (t, *J* = 7.6 Hz, 3H), 2.13 (ddq, *J* = 3.2, 6.4, 7.6 Hz, 2H), 5.62 (dt, *J* = 6.4, 6.4 Hz, 1H), 6.60 (s, 1H), 7.01 (dt, *J* = 6.4, 3.2 Hz, 1H), 7.19 (dd, *J* = 7.6, 8.0 Hz, 1H), 7.25 (dd, *J* = 7.6, 8.0 Hz, 1H), 7.34-7.39 (m, 3H), 7.47 (t, *J* = 7.6 Hz, 1H), 7.79 (d, *J* = 7.6 Hz, 2H), 8.20 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.2, 21.6, 86.4, 95.9, 109.2, 115.0, 120.3, 123.9, 124.1, 126.5, 129.0, 130.1, 133.6, 135.6, 137.3, 138.4, 206.3; IR (ATR) ν: 2965, 1945, 1446, 1368, 1171 cm^{-1}; HRMS (ESI) *m/z*: calcd for $C_{38}H_{34}N_2NaO_4S_2$ $[2M+Na]^+$ 669.1858, found 669.1866.

4.2.3. (E)-2-Ethyl-4-(1-(phenylsulfonyl)-1H-indol-2-yl)but-3-enenitrile (**4**)

A suspension of $Ni[P(OPh)_3]_4$ (25.9 mg, 0.020 mmol, 10 mol%) and 2-$PyPPh_2$ (21.1 mg, 0.080 mmol, 40 mol%) in toluene (0.20 mL) was heated at 100 °C for 10 min, and the mixture became a dark brown clear solution. After cooling to room temperature, the solution of **5a** (64.3 mg, 0.20 mmol) and acetonecyanohydrin (0.091 mL, 1.0 mmol, 5.0 equiv.) in toluene (0.30 mL) was added, and the reaction mixture was heated at 100 °C for 20 min. After cooling to room temperature, the reaction mixture was charged on silica gel column and eluted with solvent (*n*-hexane:AcOEt = 8:1) to give **4** (36.7 mg, 0.11 mmol) in 53% yield as a yellow solid. ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.15 (t, *J* = 7.6 Hz, 3H), 1.86 (dq, *J* = 7.6, 7.6 Hz, 2H), 3.43 (dt, *J* = 7.2, 7.6 Hz, 1H), 5.98 (dd, *J* = 7.2, 15.6 Hz, 1H), 6.71 (s, 1H), 7.24 (dd, *J* = 7.6, 8.0 Hz, 1H), 7.31-7.41 (m, 4H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.51 (t, *J* =

7.6 Hz, 1H), 7.74 (d, *J* = 7.6 Hz, 2H), 8.21 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 11.3, 26.5, 35.8, 109.6, 115.0, 119.6, 120.9, 124.1, 124.5, 125.2, 126.5, 127.1, 129.1, 129.5, 133.9, 137.2, 137.3, 138.2; IR (ATR) ν: 2970, 2246, 1447, 1362, 965 cm^{-1}; HRMS (ESI) *m/z*: calcd for $C_{20}H_{18}N_2NaO_2S$ $[M+Na]^+$ 373.0987, found 373.0986; mp: 112-113 °C.

4.2.4. 2-Ethyl-4-(1-(phenylsulfonyl)-1H-indol-2-yl)butanenitrile (**10**)

To a solution of **4** (101.7 mg, 0.29 mmol) in MeOH/AcOEt (2:1, 7.3 mL), Pd/C (10% Pd, 30.5 mg, 30%w/w) was added. The suspension was degassed, charged with H_2 gas and stirred vigorously for 3 h at 60 °C. The reaction mixture was cooled to room temperature, filtered through a Celite® pad eluting with AcOEt, combined eluents were concentrated in *vacuo*. The crude residue was purified by flash column chromatography (*n*-hexane:AcOEt = 9:1) to give **10** (91.8 mg, 0.26 mmol) in 90% yield as a colorless solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.10 (t, *J* = 7.6 Hz, 3H), 1.68 (dq, *J* = 7.2, 7.6 Hz, 2H), 1.98-2.07 (m, 1H), 2.09-2.17 (m, 1H), 2.50-2.57 (m, 1H), 3.08-3.16 (m, 1H), 3.26-3.33 (m, 1H), 6.48 (s, 1H), 7.23 (dd, *J* = 7.2, 7.2 Hz, 1H), 7.29 (dd, *J* = 7.2, 8.0 Hz, 1H), 7.39-7.44 (m, 3H), 7.51 (t, *J* = 7.2 Hz, 1H), 7.72 (d, *J* = 7.2 Hz, 2H), 8.17 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 11.6, 25.5, 27.1, 31.7, 32.7, 110.5, 114.9, 120.4, 121.8, 123.9, 124.4, 126.2, 129.3, 129.5, 133.8, 137.3, 138.5, 139.6; IR (ATR) ν: 2968, 2236, 1447, 1364, 728 cm^{-1}; HRMS (ESI) *m/z*: calcd for $C_{20}H_{20}N_2NaO_2S$ $[M+Na]^+$ 375.1143, found 375.1141; mp: 113-114 °C.

4.2.5.

5-((tert-Butyldimethylsilyl)oxy)-2-ethyl-2-(2-(1-(phenylsulfonyl)-1H-indol-2-yl)ethyl)pentanenitrile (**3**)

To a solution of **10** (194.7 mg, 0.55 mmol) and $TBSO(CH_2)_3I$ (198.9 mg, 0.66 mmol, 1.2 equiv.) in THF (2.8 mL), LHMDS (1.0 M in THF, 1.4 mL, 1.4 mmol, 2.5 equiv.) was added dropwise at –78 °C and the reaction mixture was allowed to be warmed to room temperature gradually. After being stirred for 12 h, the reaction mixture was added sat. NH_4Cl (3 mL) at 0 °C. The aqueous layer was extracted with AcOEt (3 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in *vacuo*. The crude residue was purified by flash column chromatography (*n*-hexane:AcOEt = 100:0 to 10:1) to give **3** (225.5 mg, 0.43 mmol) in 78% yield as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.06 (s, 6H), 0.90 (s, 9H), 1.06 (t, *J* = 7.2 Hz, 3H), 1.61-1.76 (m, 6H), 2.00-2.05 (m, 2H), 3.12-3.17 (m, 2H), 3.67 (t, *J* = 5.6 Hz, 2H), 6.45 (s, 1H), 7.21 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.20-7.31 (m, 2H), 7.38-7.42 (m, 3H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 2H), 8.17 (d,

J = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: –5.3, 8.6, 18.3, 24.8, 25.9, 27.5, 28.9, 31.9, 35.8, 40.9, 62.6, 109.8, 114.9, 120.3, 123.5, 123.8, 124.3, 126.2, 129.3, 129.6, 133.8, 137.2, 138.6, 140.5; IR (ATR) ν: 2929, 2229, 1448, 1247, 1175, 1091, 775, 727 cm^{-1}; HRMS (ESI) *m/z*: calcd for $C_{29}H_{40}N_2NaO_3SSi$ $[M+Na]^+$ 547.2427, found 547.2435.

4.2.6.

N-(5-((tert-Butyldimethylsilyl)oxy)-2-ethyl-2-(2-(1-(phenylsulfonyl)-1H-indol-2-yl)ethyl)pentyl)-2-nitrobenzenesulfonamide (**12**)

To a stirred solution of **3** (43.9 mg, 0.084 mmol) and $CoCl_2 \cdot 6H_2O$ (86.9 mg, 8.0 equiv.) in MeOH (2.8 mL), $NaBH_4$ (25.3 mg, 8.0 equiv.) was added portionwise at –20 °C. After being stirred at the same temperature for 1 h, the reaction mixture was added same amount of $CoCl_2 \cdot 6H_2O$ and $NaBH_4$ at –20 °C, and was stirred for additional 1 h. Then the reaction was quenched by the addition of sat. NH_4Cl (5 mL) at 0 °C. The aqueous layer was extracted with AcOEt (5 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in *vacuo*. To a solution of the above residue in DCM (0.84 mL) were added Et_3N (13 μL, 0.092 mmol, 1.1 equiv.) and 2-nitrobenzenesulfonyl chloride (20.5 mg, 0.092 mmol, 1.1 equiv.) at 0 °C. The reaction was quenched by the addition of sat. NH_4Cl (3 mL) at room temperature after 16 h. The aqueous layer was extracted with DCM (3 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in *vacuo*. The resulting residue was purified by flash column chromatography (*n*-hexane:AcOEt = 8:1) to give **12** (46.2 mg, 0.065 mmol) in 77% yield for 2 steps from **3** as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.05 (s, 6H), 0.81 (t, *J* = 7.2 Hz, 3H), 0.89 (s, 9H), 1.30-1.46 (m, 6H), 1.65-1.69 (m, 2H), 2.86-2.91 (m, 2H), 2.97 (d, *J* = 6.4 Hz, 2H), 3.59 (t, *J* = 6.0 Hz, 2H), 5.42 (t, *J* = 6.4 Hz, 1H), 6.38 (s, 1H), 7.19-7.27 (m, 2H), 7.37-7.41 (m, 3H), 7.50 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.61-7.67 (m, 1H), 7.69-7.72 (m, 3H), 7.77 (dd, *J* = 1.2, 7.6 Hz, 1H), 8.11-8.14 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: –5.3, 7.1, 18.3, 22.9, 25.9, 26.1, 26.5, 29.7, 33.8, 38.6, 48.0, 63.3, 109.1, 114.7, 120.2, 123.7, 124.0, 125.2, 126.1, 129.2, 129.8, 131.1, 132.7, 133.2, 133.5, 133.7, 137.1, 138.7, 141.9, 148.0; IR (ATR) ν: 3338, 2929, 1541, 1448, 1362, 1242, 1172, 1092, 728 cm^{-1}; HRMS (ESI) *m/z*: calcd for $C_{35}H_{47}N_3NaO_7S_2Si$ $[M+Na]^+$ 736.2522, found 736.2526.

4.2.7. 2-(2-(3-Ethyl-1-((2-nitrophenyl)sulfonyl)piperidin-3-yl)ethyl)-1-(phenylsulfonyl)-1H-indole (**14**)

To a solution of **12** (117.2 mg, 0.16 mmol) in THF (1.6 mL), tetrabutylammonium fluoride (1.0 M in THF, 0.33 mL, 0.33 mmol, 2.0 equiv.) was added at 0 °C. After being stirred at room temperature for 12 h, the reaction was quenched by the addition of sat. NH_4Cl (3 mL) at 0 °C. The aqueous layer was extracted with AcOEt (3 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in *vacuo*. The residue was used in the next reaction without further purification. To a solution of the above residue and PPh_3 (86.3 mg, 0.33 mmol, 2.0 equiv.) in toluene (13.4 mL), di-2-methoxyethyl azodicarboxylate (76.9 mg, 0.33 mmol, 2.0 equiv.) in toluene (3.0 mL) was added at room temperature under Ar atmosphere. After being stirred for 30 min, the reaction mixture was added H_2O (15 mL) and the aqueous layer was extracted with toluene (10 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in *vacuo*. The residue was purified by flash column chromatography (*n*-hexane:AcOEt = 3:1) to give **14** (93.9 mg, 0.16 mmol) in 98% yield for 2 steps from **12** as a colorless foam. ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 0.85 (t, *J* = 7.2 Hz, 3H), 1.39-1.45 (m, 2H), 1.46-1.53 (m, 2H), 1.68-1.80 (m, 4H), 2.83-2.93 (m, 2H), 2.98 (d, *J* = 12.6 Hz, 1H), 3.15-3.19 (m, 2H), 3.32-3.36 (m, 1H), 6.39 (s, 1H), 7.20 (dd, *J* = 7.2, 7.2 Hz, 1H), 7.26 (dd, *J* = 7.2, 7.2 Hz, 1H), 7.38-7.41 (m, 3H), 7.49-7.52 (m, 2H), 7.59 (dd, *J* = 7.2, 7.2 Hz, 1H), 7.64 (dd, *J* = 7.2, 7.2 Hz, 1H), 7.72 (d, *J* = 8.4 Hz, 2H), 7.93 (d, *J* = 7.2 Hz, 1H), 8.15 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 7.1, 21.1, 22.7, 27.2, 30.0, 33.0, 35.8, 46.8, 54.3, 109.0, 114.7, 120.2, 123.6, 124.0, 126.2, 129.2, 129.8, 130.8, 131.4, 131.7, 133.3, 133.6, 137.2, 138.9, 142.2, 148.4; IR (ATR) ν: 2932, 1546, 1449, 1371, 1175, 755 cm^{-1}; HRMS (ESI) *m/z*: calcd for $C_{29}H_{31}N_3NaO_6S_2$ $[M+Na]^+$ 604.1552, found 604.1545.

4.2.8. 2-(2-(3-Ethylpiperidin-3-yl)ethyl)-1H-indole (**2a**)

A solution of **14** (24.1 mg, 0.041 mmol) and KOH (46.5 mg, 0.83 mmol) in MeOH (0.41 mL) was heated under reflux conditions for 12 h. Then the reaction mixture was cooled to room temperature and added H_2O (2 mL). The reaction mixture was extracted with AcOEt (2 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in *vacuo*. The residue was purified by flash column chromatography (NH silica; AcOEt:MeOH = 20:1) to give **2a** (7.5 mg, 0.029 mmol) in 71% yield as a yellow oil. ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 0.86 (t, *J* = 7.8 Hz, 3H), 1.28-1.37 (m, 2H), 1.40-1.45 (m, 1H), 1.46-1.56 (m, 2H), 1.59-1.68 (m, 2H), 1.95 (ddd, *J* = 6.0, 14.4, 14.4 Hz, 1H), 2.51 (d, *J* = 12.0 Hz, 1H), 2.61-2.75 (m, 6H), 2.91-2.93 (m, 1H), 6.23 (s, 1H), 7.05 (dd,

J = 7.2, 7.2 Hz, 1H), 7.09 (dd, *J* = 7.2, 7.8 Hz, 1H), 7.30 (d, *J* = 7.8 Hz, 1H), 7.52 (d, *J* = 7.2 Hz, 1H), 8.93 (brs, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 7.2, 21.8, 22.1, 28.1, 33.1, 34.1, 34.7, 47.1, 54.9, 99.0, 110.3, 119.4, 119.6, 120.8, 128.8, 135.9, 140.5; IR (ATR) ν: 3245, 2930, 2856, 1458, 1422, 1285, 782, 749 cm^{-1}; HRMS (ESI) *m/z*: calcd for $C_{17}H_{25}N_2$ $[M+H]^+$ 257.2018, found 257.2015.

4.2.9. 1-(3-(2-(1H-Indol-2-yl)ethyl)-3-ethylpiperidin-1-yl)-2-chloroethan-1-one (**2b**)

To a stirred solution of **2a** (5.3 mg, 0.021 mmol) in DCM (0.20 mL), *i*Pr_2NEt (9.0 μL, 0.052 mmol, 2.5 equiv.) and chloroacetyl chloride (2.0 μL, 0.025 mmol, 1.2 equiv.) were added at 0 °C. After being stirred at room temperature for 30 min, the reaction was quenched by the addition of sat. NH_4Cl (2 mL) at 0 °C. The aqueous layer was extracted with DCM (2 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in *vacuo*. The residue was purified by flash column chromatography (*n*-hexane:AcOEt = 1:1) to give **2b** (4.8 mg, 0.014 mmol) in 70% yield as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 0.93 (t, *J* = 7.2 Hz, 3H), 1.38-1.53 (m, 3H), 1.61-1.69 (m, 5H), 2.65-2.70 (m, 2H), 2.78 (dt, *J* = 2.4, 12.0 Hz, 1H), 3.17-3.22 (m, 1H), 3.71 (d, *J* = 13.8 Hz, 1H), 4.14 (d, *J* = 12.0 Hz, 1H), 4.19 (d, *J* = 12.0 Hz, 1H), 4.25 (d, *J* = 12.6 Hz, 1H), 6.19 (s, 1H), 7.03 (dd, *J* = 7.2, 7.8 Hz, 1H), 7.09 (dd, *J* = 7.2, 7.8 Hz, 1H), 7.33 (d, *J* = 7.8 Hz, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 8.70 (brs, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 7.1, 22.0, 22.6, 28.5, 32.9, 34.6, 37.1, 41.2, 47.8, 50.3, 98.9, 110.6, 119.2, 119.5, 120.7, 128.6, 136.2, 140.4, 166.0; IR (ATR) ν: 2931, 1635, 1456, 1252, 747 cm^{-1}; HRMS (ESI) *m/z*: calcd for $C_{19}H_{25}ClN_2NaO$ $[M+Na]^+$ 355.1553, found 355.1559.

4.2.10. 2-(2-(3-Ethylpiperidin-3-yl)ethyl)-1-(phenylsulfonyl)-1H-indole (**15**)

A solution of **14** (65.7 mg, 0.11 mmol) in DMF (0.57 mL) with K_2CO_3 (62.5 mg, 0.45 mmol, 4.0 equiv.) and 4-*tert*-butylthiophenol (38 μL, 0.23 mmol, 2.0 equiv.) was heated at 40 °C for 12 h. Then the reaction mixture was cooled to room temperature and concentrated in *vacuo*. The resultant residue was purified by flash column chromatography (NH silica, *n*-hexane/AcOEt = 1/1 to AcOEt:MeOH = 20:1) to give **15** (44.4 mg, 0.11 mmol) in 99% yield as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.80 (t, *J* = 7.2 Hz, 3H), 1.36-1.52 (m, 5H), 1.65-1.82 (m, 3H), 2.59 (d, *J* = 12.4 Hz, 1H), 2.64 (d, *J* = 12.4 Hz, 1H), 2.72-2.81 (m, 2H), 2.86 (t, *J* = 7.6 Hz, 2H), 6.43 (s, 1H), 7.18-7.27 (m, 2H), 7.36-7.40 (m, 3H), 7.50 (t, *J* = 8.0 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 2H), 8.18 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 7.2, 22.5, 22.8, 27.6, 33.8, 34.1, 34.6, 47.2, 55.3, 108.7, 114.8, 120.1, 123.6, 123.9,

126.1, 129.2, 129.8, 133.6, 137.3, 139.1, 143.0; IR (ATR) ν: 2929, 1448, 1365, 1174, 748, 727 cm^{-1}; HRMS (ESI) *m/z*: calcd for $C_{23}H_{29}NaO_2S$ $[M+Na]^+$ 397.1950, found 397.1947.

4.2.11. 2-(2-(1-Benzyl-3-ethylpiperidin-3-yl)ethyl)-1-(phenylsulfonyl)-1H-indole (**16**)

To a solution of **15** (34.2 mg, 0.086 mmol) in DCM (0.58 mL), benzaldehyde (10.6 μL, 0.103 mmol, 1.2 equiv.) and $NaBH(OAc)_3$ (27.3 mg, 0.129 mmol, 1.5 equiv.) were added. After being stirred at room temperature for 12 h, the reaction was quenched by the addition of sat. $NaHCO_3$ (2 mL) at 0 °C. The aqueous layer was extracted with DCM (2 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in *vacuo*. The residue was purified by flash column chromatography (*n*-hexane:AcOEt = 7:1) to give **16** (7.8 mg, 0.016 mmol) in 79% yield as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.74 (t, *J* = 7.6 Hz, 3H), 1.27-1.52 (m, 4H), 1.57-1.62 (m, 2H), 1.75 (t, *J* = 8.4 Hz, 2H), 2.13 (br, 2H), 2.35 (br, 2H), 2.72-2.90 (m, 2H), 3.39 (d, *J* = 13.2 Hz, 1H), 3.46 (d, *J* = 13.2 Hz, 1H), 6.40 (s, 1H), 7.19-7.37 (m, 9H), 7.41 (d, *J* = 7.2 Hz, 1H), 7.47 (t, *J* = 7.2 Hz, 1H), 7.68 (d, *J* = 7.2 Hz, 2H), 8.18 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 7.3, 21.9, 22.7, 28.0, 33.7, 34.1, 35.9, 54.7, 62.7, 63.5, 108.4, 114.7, 120.0, 123.5, 123.8, 126.2, 126.7, 128.1, 128.8, 129.1, 129.9, 133.5, 137.3, 139.2, 129.3, 143.2; IR (ATR) ν: 2931, 1448, 1366, 1174, 744, 727 cm^{-1}; H RMS (ESI) *m/z*: calcd for $C_{30}H_{35}N_2O_2S$ $[M+Na]^+$ 487.2419, found 487.2418.

4.2.12. 2-(2-(1-Benzyl-3-ethylpiperidin-3-yl)ethyl)-1H-indole (**2c**)

A solution of **16** (3.3 mg, 0.0068 mmol) and KOH (7.6 mg, 0.136 mmol) in MeOH/THF (3:1, 0.14 mL), was heated under reflux conditions for 12 h. Then the reaction mixture was cooled to room temperature and added H_2O (3 mL). The aqueous layer was extracted with AcOEt (3 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in *vacuo*. The residue was purified by flash column chromatography (*n*-hexane:AcOEt = 10:1) to give **2c** (2.0 mg, 0.0058 mmol) in 85% yield as an orange oil. ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 0.80 (t, *J* =7.8 Hz, 3H), 1.21-1.28 (m, 2H), 1.29-1.34 (m, 1H), 1.36-1.46 (m, 2H), 1.56-1.62 (m, 1H), 1.66-1.72 (m, 2H), 1.87-2.02 (m, 2H), 2.17-2.31 (m, 2H), 2.45-2.51 (m, 1H), 2.52-2.61 (m, 2H), 3.41 (d, *J* = 12.6 Hz, 1H), 3.46 (d, *J* = 12.6 Hz, 1H), 6.22 (s, 1H), 7.05 (dd, *J* = 7.2, 7.2 Hz, 1H), 7.09 (dd, *J* = 7.2, 7.2 Hz, 1H), 7.23-7.27 (m, 2H), 7.30-7.34 (m, 4H), 7.52 (d, *J* = 7.2 Hz, 1H), 8.02 (brs, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 7.3, 21.92, 21.94, 28.6, 29.7, 33.9, 35.7, 55.0, 62.2, 63.4, 99.0, 110.2, 119.5, 119.6, 120.8,

126.9, 128.1, 128.8, 128.9, 135.8, 139.1, 140.7; IR (ATR) ν: 3407, 2931, 2856, 1456, 1288, 779, 744, 699 cm^{-1}; HRMS (ESI) *m/z*: calcd for $C_{24}H_{31}N_2$ $[M+H]^+$ 347.2487, found 347.2481.

Acknowledgements

This research was supported by a JSPS KAKENHI Grant (21590003), The Uehara Memorial Foundation and The Naito Foundation (to S.A.).

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17. See supporting information

Supplementary Material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/