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Chiral Holmium Complex-Catalyzed Synthesis of Hydrocarbazole from Siloxyvinylindole and Its Application to the Enantioselective Total Synthesis of (−)-Minovincine

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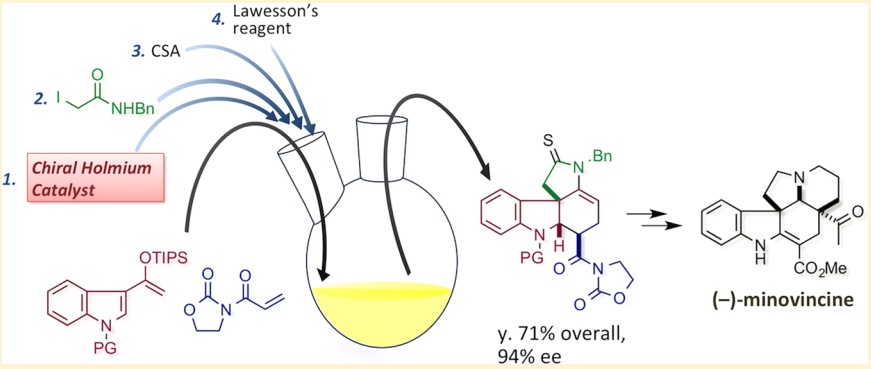
Supporting Information



ABSTRACT: The catalytic and enantioselective total synthesis of (−)-minovincine has been accomplished. The key highly substituted hydrocarbazole derivative was obtained by an asymmetric Diels−Alder reaction of siloxyvinylindole catalyzed by 0.5 mol % of a chiral holmium complex. The Diels−Alder adduct was converted to a tetracyclic intermediate in a one-pot procedure. No waste stereoisomers were produced throughout the entire total synthesis.

The pentacyclic framework that is composed of an indolizidine-fused hydrocarbazole with several continuous stereocenters is a prominent structural element that is found in a large number of indole alkaloids (Figure 1), such as minovincine (**1**, *vinca*), spegazzinine (**2**, *aspidosperma*), and kopsinine (**3**, *kopsia*).[1] Some indole alkaloids have high-profile biological activities and could be valuable leads to clinically useful medicines: vinblastine and vincristine.[2] The remarkable potential of indole alkaloids as therapeutic agents and their unique structures has attracted the attention of synthetic chemists, and various unique approaches to constructing the pentacyclic framework have been reported,[3] including catalytic asymmetric syntheses.[4] To support both the search for new drug candidates and the investigation of structure−activity relationships, versatile and practical enantioselective methods for accessing common pentacyclic skeletons with different substitution patterns are required.[5]

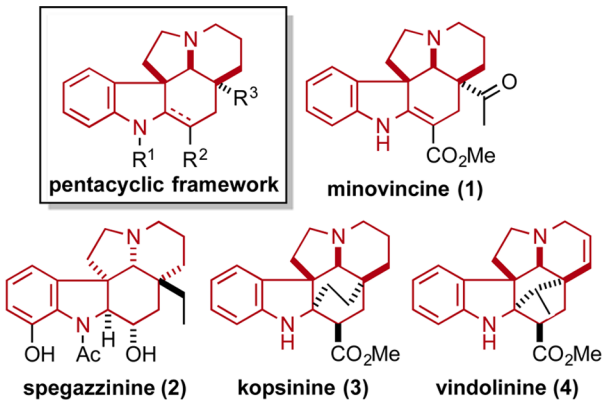


Figure 1. Representative indole alkaloids with a pentacyclic framework.

We recently reported a new method for the synthesis of optically active hydrocarbazoles possessing a quaternary carbon at the 4a position in 2 steps through a Diels−Alder reaction of siloxyvinylindole **5** using a chiral holmium/bisthiourea catalyst and alkylation of the silyl enol ether of Diels−Alder product **6** (Scheme 1).[6] This sequential process could provide a versatile synthesis of hydrocarbazole derivatives **7**, since both intermolecular reactions have a broad scope.[7] Moreover, the quaternary carbon at the 4a position of the hydrocarbazole skeleton is a common structural feature in a wide range of indole alkaloids.[8] Here we report the stereoselective construction of the pentacyclic hydroindolizinocarbazole framework and demonstrate the utility of our methodology for natural product synthesis by the catalytic and enantioselective total synthesis of (−)-minovincine (**1**),[9−12] which is considered to be a biogenetic link between the kopsinine (**3**) and

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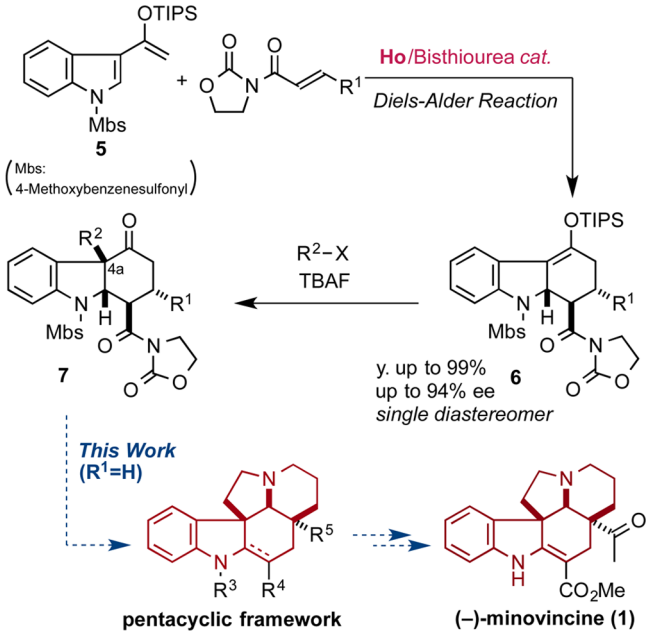
Scheme 1. Concise and Stereoselective Synthesis of Chiral Hydrocarbazoles and Their Transformation



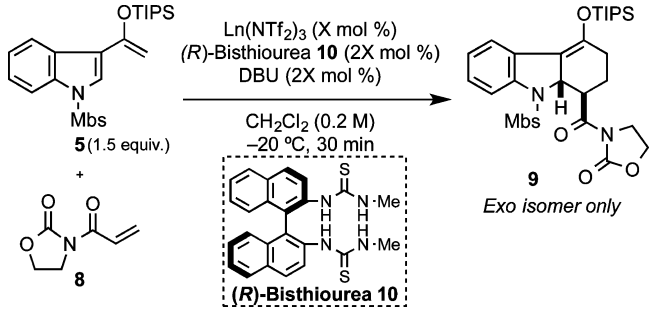
vindolinine (**4**) classes of alkaloids[8] and can be transformed to other alkaloid families.[10a,13]

Our synthesis began with Diels–Alder reaction of siloxyvinylindole **5** and acrylate derivative **8** to give *exo* adduct **9**.[14] Although $Ho(NTf_2)_3$ was revealed to be the best Lewis acid in combination with bisthiourea ligand **10** based on its activation profile with a wide range of dienophiles,[6] the best lanthanide salt for enhancing the enantiomeric excess of the product depends on the substrate structure.[7,15] Therefore, we briefly surveyed lanthanide salts in the Diels–Alder reaction using **5** and **8** (Table 1). As the atomic number of the lanthanide metal increased, the enantioselectivity also tended to increase (Table 1, entries 1–10, and Figure 2), and lutetium salt gave the highest enantioselectivity under a catalyst loading of 5 mol % (entry 10, Table 1). However, a decrease in the amount of lutetium salt lowered the enantioselectivity (entries 10 and 11; 90% ee vs 84% ee) due to instability of the chiral catalyst. On the other hand, 1 mol % of holmium salt (entry 13) gave a result similar to the reaction using 5 mol % catalyst (entry 6). Moreover, even 0.5 mol % of the catalyst at a 10 mmol scale of substrate **8** was sufficient to complete the reaction under rigorously dehydrated conditions (entry 14).

Treatment of silyl enol ether **9** with *N*-benzyliodoacetamide[16] and TBAF furnished a tetracyclic compound **11** with a quaternary carbon center as a single diastereomer (Scheme 2). Subsequent dehydration under acidic conditions afforded enamide **12**. Thiocarbonylation using Lawesson's reagent gave thioamide **13**.

These sequential processes could proceed in a one-pot reaction. A Diels–Alder reaction was performed at a 10 mmol scale, and the Diels–Alder adduct was converted to thioamide **13** via alkylation, dehydration, and thiocarbonylation in a single flask without purification of the intermediates (Scheme 3). The optical purity of thioamide **13** was enriched to be 94% ee after a single recrystallization. Our holmium-catalyzed reaction and sequential transformation realized a practical approach to chiral tetracyclic synthetic intermediates as well as a construction of chiral hydrocarbazoles.

Table 1. Screening of Lanthanide Salts in the Asymmetric Diels–Alder Reaction



entry	Ln	X	yield (%)	% ee
1	Sm	5	90	75
2	Eu	5	89	78
3	Gd	5	94	80
4	Tb	5	91	80
5	Dy	5	90	80
6[a]	Ho	5	95	86
7	Er	5	98	83
8	Tm	5	94	84
9	Yb	5	92	86
10	Lu	5	96	90
11	Lu	2	99	84
12	Ho	2	99	86
13[b]	Ho	1	90	87
14[b,c]	Ho	0.5	98	87

[a]Data reported in our previous paper.[6] [b]1.1 equiv of diene **5** were used. Reaction was performed at 0 °C for 1 h. [c]10 mmol (>1.4 g) of **8** were used. MS4 Å (50 mg/1.0 mL CH_2Cl_2) was added to the reaction mixture.

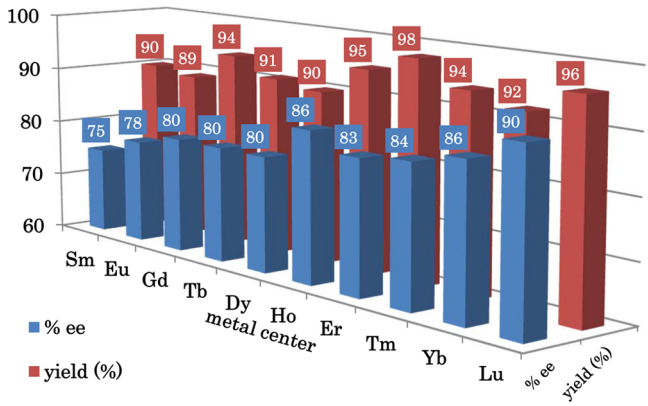


Figure 2. Yield and enantiomeric excess of the product **9** using each lanthanide imidate.

The oxazolidinone moiety was converted to thioester **14** in 67% yield by the reaction with LiSEt[17] (Scheme 4). Successful X-ray crystallographic analysis of optically pure **14** unambiguously confirmed the relative and absolute configurations.[18] Subsequent reductions using $LiAlH_4$ gave enamine **15** with a trace amount of over-reduced byproduct. Conversion of γ-lactam to pyrrolidine through thiolactam was essential. All efforts for the direct synthesis of enamine **15** through the reduction of **12**, **13**, or related compounds failed due to an extremely low yield of **15**, which resulted from partial reduction of the oxazolidone ring or over reduction of the enamine. Acetylation of enamine **15** gave α,β-unsaturated ketone **16**.

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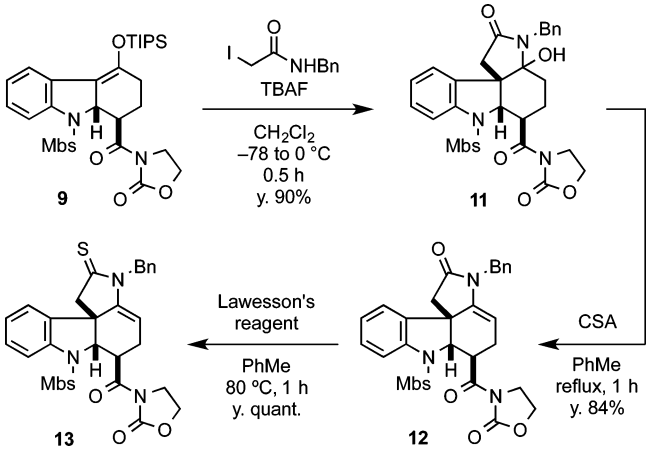
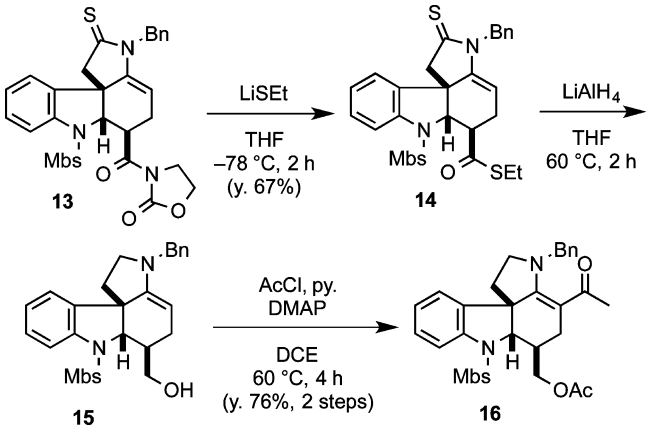
Scheme 2. Transformation to Chiral Tetracyclic Intermediates



Scheme 4. Conversion to a Hydropyrrolocarbazole Skeleton



This tetrasubstituted olefin was then stereoselectively reduced. Most indole alkaloids with a pentacyclic framework have a cis-oriented pyrrolidine ring. The PtO_2-catalyzed heterogeneous hydrogenation[19] of tetrasubstituted olefin of **16** proceeded smoothly. However, nuclear Overhauser effect experiments revealed that the obtained product had an undesired trans-fused pyrrolidine **17b** (entry 1, Table 2). Similarly, 1,4-reduction of enone **16** with $LiAlH_4$[20] or $NiCl_2$/$NaBH_4$[21] produced **17b** exclusively (entries 2 and 3), since the β-face of the double bond seemed to be convex, as seen in the structure of **14**.[18] Treatment of enone **16** with Meerwein's reagent gave conjugated iminium enol ether, which could be reduced by $NaBH_4$.[22] These sequential transformations resulted in the generation of a trans-fused pyrrolidine ring (entry 4). The reduction using $NaBH(OAc)_3$[23] produced **17a** with a cis-fused pyrrolidine ring in low yield as a minor product (entry 5). These reductions (entries 1−5) proceeded through the delivery of hydride or hydrogen from the convex face. Finally, enone **16** was treated with pinacolborane to give the cis-fused pyrrolidine ring exclusively (entry 6). Since the pinacolborane-mediated reduction of **16** gave borane enolate, we added K_2CO_3 and methanol to the crude mixture to quench the reaction and decompose borane enolate to give cis-fused pyrrolidine **18**.[24]

The mechanism of this pinacolborane-mediated stereoselective reduction would be as follows. First, the tertiary amine formed a complex with pinacolborane (Figure 3, **A**), after which pinacolborane activated the β-amino-α,β-unsaturated ketone (**B**),[25] and this was followed by intramolecular delivery of the hydride to iminium cation through six-membered transition state **C**.[26] A boat conformation of the cyclohexane ring realized the attack of hydride from the α-face, which led to selective production of the desired borane enolate **D**.

Further transformations of primary alcohol by sequential IBX oxidation, Pinnick oxidation, and esterification afforded methyl ester **21** in good yields (Scheme 5). During these transformations, epimerization of the acetyl group was observed. This was not a concern, however, because both diastereomers could be converged into a single compound in a later step. Therefore, we pursued construction of the pentacyclic framework.

The benzyl group of **21** was removed by hydrogenation with $PdCl_2$. Treatment of the secondary amine **22** with 1,3-diiodopropane and $NaHCO_3$ in DMF provided a labile iodide **23** that could be converted to pentacyclic compound **24** by exposure to strong basic conditions. Transformation to **24** using secondary amine **22** could be a one-pot procedure by modifying the conditions reported by MacMillan's group.[12] The yield of piperidine ring formation was lower than that of MacMillan's report (Scheme 6). This was because the formation of allylamine derivative and/or hydrolysis of the methyl ester were inevitable.[27]

Next, we explored the conditions for Mbs deprotection. A nucleophilic substitution reaction with phosphide anions advanced the deprotection reaction.[28] $KPPh_2$-mediated deprotection of *N*-sulfonamide group followed by the conversion of carboxylic acid, which was partially hydrolyzed under the reaction conditions, to methyl ester using $TMSCHN_2$ gave

Scheme 3. One-Pot Synthesis of Chiral Tetracyclic Intermediate

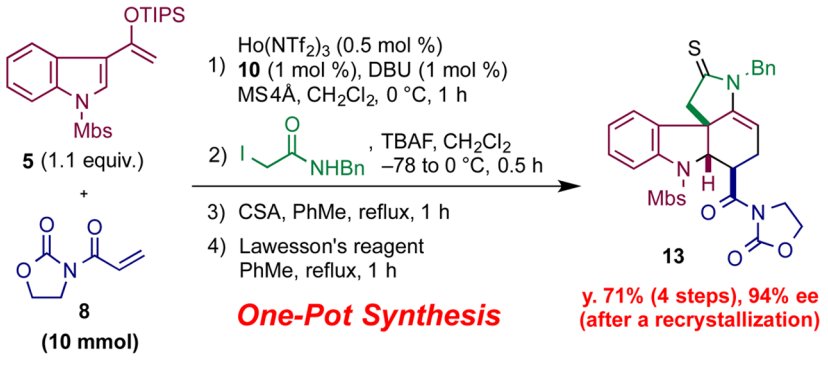


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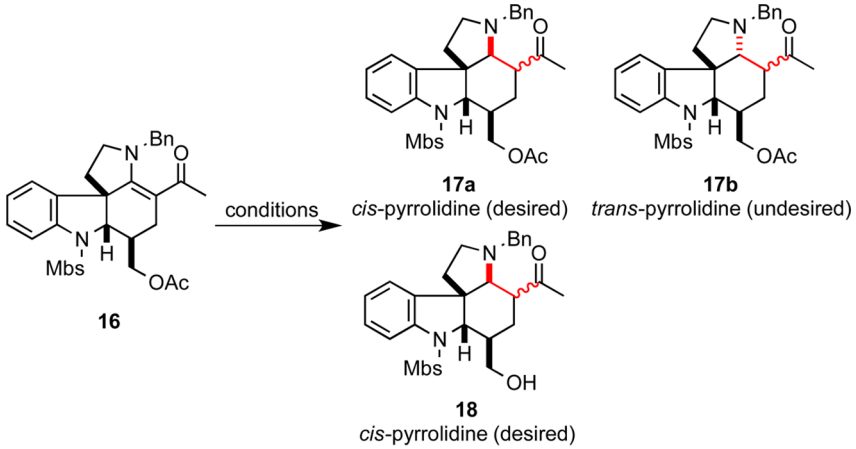
Table 2. Stereoselective Reduction of Tetrasubstituted Olefin



entry	conditions	product: yield
1	PtO_2, H_2 (1 atm), EtOH, rt, 17 h	**17b**: 95%
2	$LiAlH_4$, THF, −78 to −40 °C, 3 h	**17b**: 72%
3	$NiCl_2$, $NaBH_4$, THF/MeOH, −40 to 0 °C, 1 h	**17b**: 30%, **16**: 70%
4	Et_3OBF_4, CH_2Cl_2, rt, 3 h; then $NaBH_4$, CH_2Cl_2/MeOH, −78 to 0 °C, 30 min	**17b**: quant.
5	$NaBH(OAc)_3$, AcOH, rt, 3 h	**17a**: 5%, **17b**: 20%
6	PinBH, THF, −78 to −40 °C, 1 h; then K_2CO_3, THF/MeOH, rt, 3 h	**18**: 75%[a]

[a]No *trans*-isomer was observed in the ^{1}H NMR spectrum of the crude borane enolate intermediate.

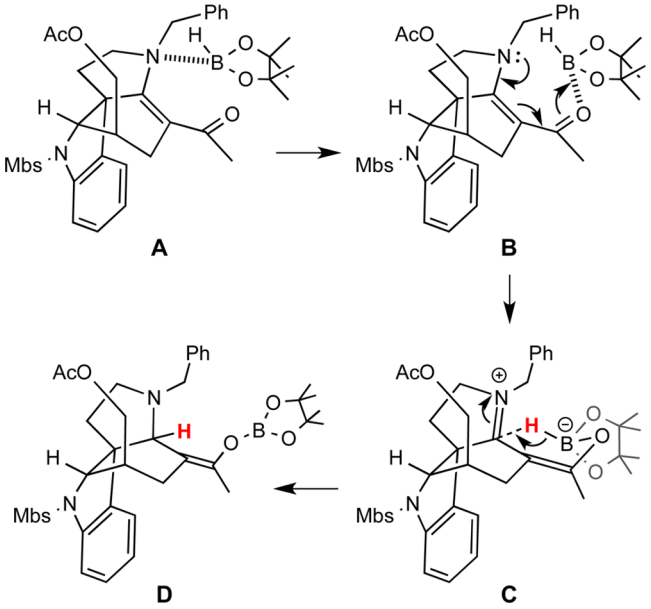
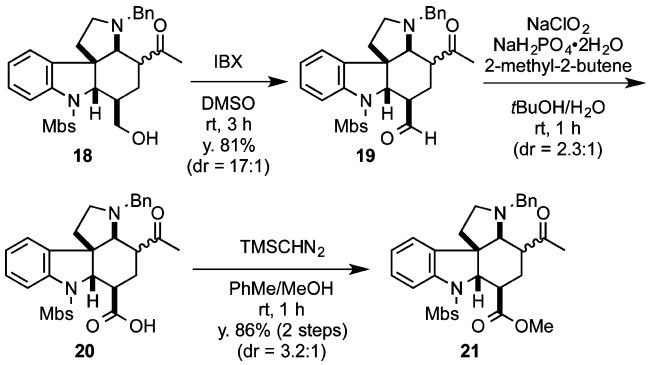


Figure 3. Proposed mechanism of pinacolborane-mediated reduction.

Scheme 5. Construction of cis-Oriented Pyrrolidine



25.[29] Finally, DDQ oxidation of **25** gave (−)-minovincine (**1**) in 41% yield (Scheme 7). The spectral data of synthetic (−)-minovincine were in agreement with those of the natural isolate[9a] and MacMillan's synthetic (−)-minovincine.[12]

In conclusion, we have demonstrated a simple and straightforward procedure for the highly enantio- and diastereoselective construction of a pentacyclic framework common to indole alkaloids. Our efforts also led to a second enantioselective total synthesis of (−)-minovincine. The most remarkable aspect of our total synthesis is that no undesired diastereomers were generated.

EXPERIMENTAL SECTION

General Information. NMR spectra were recorded at 400 or 600 MHz for ^{1}H NMR and at 100 or 150 MHz for ^{13}C NMR. Chemical shifts for proton are reported in parts per million downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CDCl_3$ δ: 7.26 ppm). For ^{13}C NMR, chemical shifts were reported in the scale relative to the NMR solvent ($CDCl_3$ δ: 77.0 ppm) as an internal reference. Infrared spectra were recorded on an ATR. Optical rotations were measured at 589 nm. Mass spectra were recorded using ESI mode with TOF analyzer. The enantiomeric excess (ee) was determined by HPLC analysis measured at 254 nm with a chiral column (Chiralcel IA). X-ray crystallographic data were collected at −180 ± 1 °C using filtered Cu−Kα radiation. Reactions were carried out in dry solvents under an argon atmosphere, unless otherwise noted. Dry CH_2Cl_2 for catalyst was purchased from a commercial supplier. (*R*)-(+)-1,1′-Binaphthyl-2,2′-diamine was purchased from a commercial supplier. Lanthanide trifluoromethanesulfonimides ($Ln(NTf_2)_3$) were synthesized by following the procedure reported in the literature.[30] MS4 Å was purchased from a commercial supplier (powder, −325 mesh particle size). Other solvents and reagents were purified by usual methods. Flash column chromatog-

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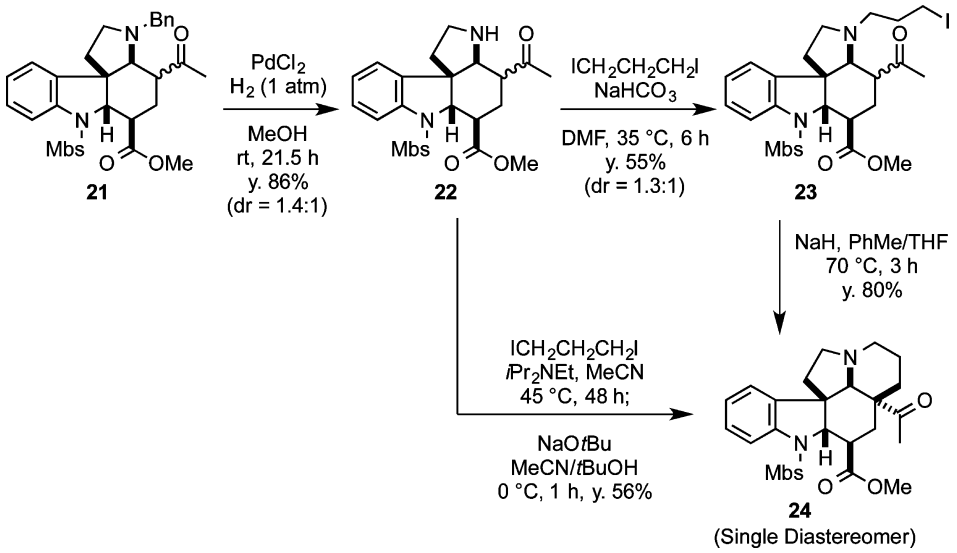
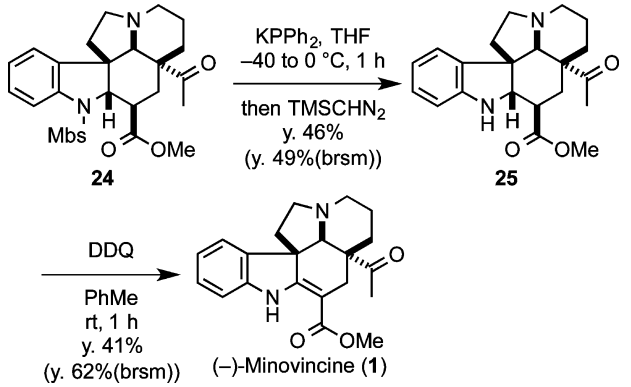
Scheme 6. Construction of the Piperidine Ring



Scheme 7. Total Synthesis of (−)-Minovincine



raphy was performed on silica gel, 60 μm particle, unless otherwise noted.

*One-Pot 4-Step Procedure for the Synthesis of **13**. First Step: 3-((1R,9aS)-9-((4-Methoxyphenyl)sulfonyl)-4-((triisopropylsilyl)oxy)-2,3,9,9a-tetrahydro-1H-carbazole-1-carbonyl)oxazolidin-2-one (**9**).*[6] $Ho(NTf_2)_3$ (50.2 mg, 50 μmol, 0.5 mol %), bisthiourea **10** (43.1 mg, 100 μmol, 1 mol %), and dried MS4 Å (2.5 g) taken in a 100 mL flask with a stirring bar were heated at 115 °C under reduced pressure (<0.01 mmHg) for 30 min. After being allowed to cool to rt, the flask was charged with dry argon. CH_2Cl_2 (5.0 mL) and DBU (15 μL, 100 μmol, 1 mol %) were added successively. After the resulting solution was stirred for 2 h at room temperature under Ar, the reaction mixture was cooled to −20 °C. A solution of diene **5** (5.3 g, 11 mmol, 1.1 equiv) in CH_2Cl_2 (16 + 10 mL to rinse) was added, and this was followed by the addition of a solution of dienophile **8** (1.41 g, 10 mmol) in CH_2Cl_2 (12.5 + 6.5 mL to rinse). After this addition, the solution was warmed to 0 °C and stirred for 1 h under Ar.

The product could be isolated by flash column chromatography (CHROMATOREX-NH, hexane/AcOEt = 3.5/1) in 98% yield and 87% ee as a colorless foam. For details on the workup process and spectral data of **9**, see ref 6.

*Second Step: 3-((3aR,6R,6aS,11bS)-3-Benzyl-3a-hydroxy-7-((4-methoxyphenyl)sulfonyl)-2-oxo-2,3,3a,4,5,6,6a,7-octahydro-1H-pyrrolo[2,3-d]carbazole-6-carbonyl)oxazolidin-2-one (**11**).* After the Diels−Alder reaction was complete, *N*-benzyliodoacetamide (3.85 g, 14 mmol, 1.4 equiv) was added to the reaction mixture in one portion. After the mixture was cooled to −78 °C, TBAF (14 mL, 14 mmol, 1.4 equiv., 1.0 M in THF) was added dropwise. The solution was warmed to 0 °C over 30 min under Ar.

The product could be isolated by standard workup followed by flash column chromatography (SiO_2, hexane/AcOEt = 1/2) in 90% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.45 (d, *J* = 16.8 Hz, 1H), 1.64−1.74 (m, 2H), 1.82−1.88 (m, 1H), 1.97 (d, *J* = 16.8 Hz, 1H), 2.00−2.04 (m, 1H), 2.38 (br, 1H), 3.81 (s, 3H), 3.99 (dd, *J* = 9.2, 10.0 Hz, 1H), 4.06 (d, *J* = 10.0 Hz, 1H), 4.17 (d, *J* = 14.8 Hz, 1H), 4.25−4.33 (m, 2H), 4.42 (ddd, *J* = 4.0, 10.0, 10.0 Hz, 1H), 4.53 (ddd, *J* = 10.0, 10.0, 10.0 Hz, 1H), 4.82 (d, *J* = 14.8 Hz,1H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.99 (dd, *J* = 6.8, 7.6 Hz, 1H), 7.29−7.38 (m, 7H), 7.63 (d, *J* = 8.8 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.9, 29.9, 41.4, 42.6, 43.5, 44.1, 54.9, 55.6, 62.3, 71.4, 92.4, 114.5, 117.8, 124.9, 125.5, 128.5, 128.9, 129.0, 129.4, 132.2, 137.7, 140.8, 145.8, 151.5, 153.6, 163.7, 172.7, 173.8; IR (neat): 3004, 2970, 1738, 1364, 1217 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{32}H_{31}N_3Na_1O_8S_1$ [M + H]$^+$: 640.1729, found 640.1718; $[\alpha]_D^{26}$ − 80.1 (*c* 1.00, $CHCl_3$).

*Third Step; 3-((6R,6aS,11bS)-3-Benzyl-7-((4-methoxyphenyl)-sulfonyl)-2,3,5,6,6a,7-hexahydro-1H-pyrrolo[2,3-d]carbazole-6-carbonyl)oxazolidin-2-one (**12**).* After the alkylation of **9** was complete, the volatile materials were removed under reduced pressure. The mixture was then azeotropically dried with one portion of anhydrous toluene. The mixture was refluxed with CSA (1.6 g, 7.0 mmol, 0.7 equiv) in toluene (50 mL) for 1 h using a Dean−Stark apparatus.

The product could be isolated and purified by flash column chromatography (SiO_2, hexane/AcOEt = 1/2) in 84% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.73 (d, *J* = 16.4 Hz, 1H), 2.22 (ddd, *J* = 4.0, 4.0, 16.8 Hz, 1H), 2.55 (ddd, *J* = 1.6, 8.0, 16.8 Hz, 1H), 2.73 (d, *J* = 16.8 Hz, 1H), 3.69 (ddd, *J* = 6.0, 9.6, 9.6 Hz, 1H), 3.82 (s, 3H), 4.04 (ddd, *J* = 9.6, 9.6, 9.6 Hz, 1H), 4.31 (ddd, *J* = 1.6, 4.0, 4.0 Hz, 1H), 4.34 (ddd, *J* = 9.6, 9.6, 9.6 Hz, 1H), 4.45 (ddd, *J* = 6.0, 9.6, 9.6 Hz, 1H), 4.56 (d, *J* = 15.2 Hz, 1H), 4.59 (d, *J* = 4.0 Hz, 1H), 4.67 (dd, *J* = 4.0, 8.0 Hz, 1H), 4.76 (d, *J* = 15.2 Hz, 1H), 6.73 (d, *J* = 8.0 Hz, 1H), 6.86 (d, *J* = 9.2 Hz, 2H), 6.96 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.18 (d, *J* = 6.8 Hz, 2H), 7.23−7.28 (m, 3H), 7.53 (d, *J* = 9.2 Hz, 2H), 7.68 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.5, 42.5, 43.7, 45.4, 47.8, 55.6, 62.1, 68.1, 94.4, 114.2, 116.9, 121.9, 126.0, 127.3, 127.4, 127.8, 129.0, 129.3, 135.4, 137.1, 141.0, 144.3, 152.6, 163.6, 172.2, 173.7; IR (neat): 3006, 1777, 1711, 1673, 1356, 1218, 1161 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{32}H_{29}N_3Na_1O_7S_1$ [M + Na]$^+$: 622.1624, found 622.1639; $[\alpha]_D^{24}$ − 48.6 (*c* 1.11, $CHCl_3$).

*Fourth Step; 3-((6R,6aS,11bS)-3-Benzyl-7-((4-methoxyphenyl)-sulfonyl)-2-thioxo-2,3,5,6,6a,7-hexahydro-1H-pyrrolo[2,3-d]-carbazole-6-carbonyl)oxazolidin-2-one (**13**).* After the mixture was cooled to room temperature, Lawesson's reagent (4.4 g, 14 mmol, 1.4 equiv) was added. The resulting solution was stirred at 100 °C for 1 h and then filtered through a pad of Celite that was washed with

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CH_2Cl_2. After the mixture was concentrated under reduced pressure, the title compound was isolated by flash column chromatography (CHROMATOREX-DIOL, hexane/AcOEt = 3/1 to 1/1, and then to 1/2) to give **13** (4.8 g) as an amorphous solid, which was recrystallized from hot toluene to afford **13** (4.37 g, 7.1 mmol, 94% ee) in 71% yield from the mother liquid, and a precipitate (431 mg, 18% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.26 (ddd, J = 4.0, 4.0, 16.8 Hz, 1H), 2.42 (d, J = 17.6 Hz, 1H), 2.62 (ddd, J = 2.0, 8.4, 16.8 Hz, 1H), 3.25 (d, J = 17.6 Hz, 1H), 3.68 (ddd, J = 6.4, 7.2, 9.6 Hz, 1H), 3.84 (s, 3H), 4.04 (ddd, J = 8.0, 9.6, 9.6 Hz, 1H), 4.32 (ddd, J = 7.2, 8.0, 9.6 Hz, 1H), 4.37 (dd, J = 2.0, 4.0 Hz, 1H), 4.44 (ddd, J = 7.2, 9.6, 9.6 Hz, 1H), 4.58 (br, 1H), 4.92 (dd, J = 4.0, 8.4 Hz, 1H), 5.00 (d, J = 15.2 Hz, 1H), 5.36 (d, J = 15.2 Hz, 1H), 6.67 (d, J = 7.6 Hz, 1H), 6.88 (d, J = 11.2 Hz, 2H), 6.94 (dd, J = 7.2, 7.6 Hz, 1H), 7.21−7.29 (m, 5H), 7.56 (d, J = 11.2 Hz, 2H), 7.68 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.5, 42.4, 47.4, 47.8, 49.6, 55.6, 57.1, 62.1, 67.6, 98.3, 114.3, 116.6, 122.2, 125.9, 127.3, 127.6, 127.7, 128.5, 129.1, 129.2, 134.3, 136.3, 140.6, 147.4, 152.7, 163.7, 173.4, 200.1; IR (neat): 2897, 1781, 1680, 1496 cm^{-1}; HRMS (ESI): m/z calcd for $C_{32}H_{29}N_3Na_1O_6S_2$ $[M + Na]^+$: 638.1396, found 638.1400; $[\alpha]_D^{25}$ − 72.4 (c 1.00, $CHCl_3$); Chiralcel IA, hexane/iPrOH = 70/30, f: 1.0 mL/min, 254 nm, 15.3 min (major), 22.8 min (minor).

*S-Ethyl(6R,6aS,11bS)-3-benzyl-7-((4-methoxyphenyl)sulfonyl)-2-thioxo-2,3,5,6,6a,7-hexahydro-1H-pyrrolo[2,3-d]carbazole-6-carbothioate (**14**).* A THF solution of LHMDS (15 mL, 15 mmol, 3.0 equiv) was added to a solution of **13** (3.07 g, 5.0 mmol, 87% ee) and EtSH (1.44 mL, 20 mmol, 4.0 equiv) in THF (25 mL, 0.2 M) at −78 °C under Ar. After the solution was stirred for 2 h at −78 °C, the reaction was quenched with 1.0 M aq. HCl. The mixture was warmed to room temperature, and solid $NaHCO_3$ was added to adjust the pH to neutral. The aqueous layer was extracted three times with AcOEt. The combined organic layers were dried over Na_2SO_4, filtered through a pad of Celite, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, hexane/AcOEt = 7/1 to 5/1) to afford **14** (1.98 g, 67%) as a colorless solid. A crystal for X-ray crystallographic analysis was obtained from EtOH/AcOEt. Melting Point: 176 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.20 (t, J = 7.2 Hz, 3H), 2.23 (ddd, J = 3.2, 3.2, 16.4 Hz, 1H), 2.47 (d, J = 17.2 Hz, 1H), 2.61 (ddd, J = 1.2, 8.0, 16.4 Hz, 1H), 2.83 (dq, J = 3.2, 7.6 Hz, 2H), 3.16 (d, J = 17.2 Hz, 1H), 3.62 (ddd, J = 1.2, 3.2, 3.2 Hz, 1H), 3.85 (s, 3H), 4.80 (s, 1H), 5.08 (d, J = 17.2 Hz, 1H), 5.11 (dd, J = 3.2, 8.0 Hz, 1H), 5.26 (d, J = 17.2 Hz, 1H), 6.88 (d, J = 7.6 Hz, 1H), 6.90 (d, J = 8.8 Hz, 2H), 6.94 (dd, J = 7.6, 7.6 Hz, 1H), 7.22−7.31 (m, 6H), 7.69 (d, J = 8.8 Hz, 2H), 7.70 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.5, 23.2, 23.3, 47.8, 49.0, 55.5, 55.9, 56.8, 66.8, 77.2, 99.8, 114.2, 116.3, 122.1, 125.8, 127.2, 127.6, 128.5, 129.0, 129.2, 134.2, 136.1, 140.5, 147.1, 163.7, 199.7, 200.3; IR (neat): 2969, 2355, 1683, 1665, 1592, 1353, 1152 cm^{-1}; HRMS (ESI): m/z calcd for $C_{31}H_{30}N_2Na_1O_4S_3$ $[M + Na]^+$: 613.1265, found 613.1270; $[\alpha]_D^{25}$ − 71.2 (c 0.98, $CHCl_3$); Chiralcel IA, hexane/iPrOH = 90/10, f: 1.0 mL/min, 254 nm, 12.3 min (minor), 16.1 min (major).

*((6R,6aS,11bS)-3-Benzyl-7-((4-methoxyphenyl)sulfonyl)-2,3,5,6,6a,7-hexahydro-1H-pyrrolo[2,3-d]carbazol-6-yl)methanol (**15**).* $LiAlH_4$ (228 mg, 6.0 mmol, 2.0 equiv) was added to a solution of **14** (1.79 g, 3.0 mmol, 87% ee) in THF (60 mL, 0.05 M) at 0 °C. After the mixture was stirred for 2 h at 60 °C under Ar, the mixture was cooled to 0 °C. A saturated aqueous solution of Rochelle's salt was added to the mixture slowly, and then the mixture was stirred for 1 h at rt. The aqueous layer was extracted three times with AcOEt. The combined organic layers were dried over Na_2SO_4, filtered through a plug of cotton, and concentrated under reduced pressure to give **15** as a crude product, which could be used in the next step without further purification. Spectral data for purified **15**; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.02 (ddd, J = 3.2, 8.4, 12.0 Hz, 1H), 1.37 (ddd, J = 3.2, 9.2, 12.0 Hz, 1H), 1.59−1.70 (m, 2H), 1.80 (ddd, J = 7.2, 12.0, 12.0 Hz, 1H), 1.98 (ddd, J = 9.2, 10.0, 12.0 Hz, 1H), 2.19 (br, 1H), 2.62 (ddd, J = 3.2, 9.2, 12.0 Hz, 1H), 2,91 (ddd, J = 6.4, 12.0, 12.0 Hz, 1H), 3.52 (d, J = 14.0 Hz, 1H), 3.78 (s, 3H), 3.95 (d, J = 8.8 Hz, 1H), 4.07 (ddd, J = 3.2, 3.2, 9.2 Hz, 1H), 4.13 (d, J = 14.0 Hz, 1H), 4.17 (d, J = 3.2 Hz, 1H), 6.83 (d, J = 9.2 Hz, 2H), 7.05 (dd, J = 7.2, 7.2 Hz, 1H), 7.25−7.27 (m, 3H), 7.31−7.32 (m, 4H), 7.16 (d, J = 9.2 Hz, 2H), 7.69 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 18.3, 26.1, 33.1, 36.2, 49.6, 51.2, 55.5, 58.0, 67.5, 70.9, 93.1, 99.9, 114.0, 115.6, 124.9, 125.3, 126.7, 128.2, 128.3, 129.0, 129.1, 138.0, 139.8, 142.0, 162.2; IR (neat): 2940, 1856, 2361, 1739, 1594, 1352, 1258, 1160 cm^{-1}; HRMS (ESI): m/z calcd for $C_{29}H_{31}N_2O_4S_1$ $[M + H]^+$: 503.2004, found 503.1995; $[\alpha]_D^{23}$ − 93.3 (c 1.03, $CHCl_3$).

*((6R,6aS,11bS)-4-Acetyl-3-benzyl-7-((4-methoxyphenyl)sulfonyl)-2,3,5,6,6a,7-hexahydro-1H-pyrrolo[2,3-d]carbazol-6-yl)methyl acetate (**16**).* Acetyl chloride (1.1 mL, 15 mmol, 5.0 equiv) was added to a mixture of **15** (∼3.0 mmol), DMAP (18.3 mg, 0.15 mmol, 5 mol %), and pyridine (1.2 mL, 15 mmol, 5.0 equiv) in DCE (15 mL, 0.2 M) at 0 °C. After being stirred for 4 h at 60 °C, the mixture was cooled to 0 °C. To the reaction mixture was added aq. $NaHCO_3$, and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and filtered through a plug of cotton. After the solvent was evaporated, the crude product was purified by flash column chromatography (CHROMATOREX-DIOL, hexane/AcOEt = 3/1 to 1.5/1) to give **16** (1.34 g, 76%, 2 steps) as an amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.87 (dd, J = 6.0, 12.0 Hz, 1H), 1.60 (ddd, J = 9.2, 12.0, 12.0 Hz, 1H), 2.01 (s, 3H), 2.11 (dd, J = 3.6, 15.6 Hz, 1H), 2.15 (s, 3H), 2.49 (dd, J = 1.2, 15.6 Hz, 1H), 2.69 (ddddd, J = 1.2, 2.4, 3.6, 6.0, 6.0 Hz, 1H), 3.24 (dd, J = 9.2, 12.0 Hz, 1H), 4.50 (ddd, J = 6.4, 12.0, 12.0 Hz, 1H), 3.76 (dd, J = 6.0, 11.2 Hz, 1H), 3.80 (s, 3H), 4.04 (d, J = 2.4 Hz, 1H), 4.06 (dd, J = 6.0, 11.2 Hz, 1H), 4.72 (d, J = 14.8 Hz, 1H), 4.80 (d, J = 14.8 Hz, 1H), 6.55 (d, J = 8.8 Hz, 1H), 6.86 (d, J = 9.2 Hz, 2H), 6.91 (dd, J = 6.4, 8.4 Hz, 1H), 7.20−7.23 (m, 2H), 7.27−7.31 (m, 4H), 7.59 (d, J = 9.2 Hz, 2H), 7.68 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.1, 25.8, 29.0, 37.9, 42.3, 51.3, 54.8, 55.6, 56.8, 64.3, 70.5, 77.2, 98.3, 114.1, 116.4, 123.1, 125.2, 127.6, 128.6, 128.9, 129.0, 129.1, 135.8, 136.8, 141.3, 156.6, 163.3, 171.3, 194.3; IR (neat): 2970, 1354, 1227, 1158, 1092, 1024 cm^{-1}; HRMS (ESI): m/z calcd for $C_{33}H_{35}N_2O_6S_1$ $[M + H]^+$: 587.2216, found 587.2207; $[\alpha]_D^{25}$ + 133.4 (c 1.02, $CHCl_3$).

*1-((3aS,6R,6aS,11bR)-3-Benzyl-6-(hydroxymethyl)-7-((4-methoxyphenyl)sulfonyl)-2,3,3a,4,5,6,6a,7-octahydro-1H-pyrrolo-[2,3-d]carbazol-4-yl)ethan-1-one (**18**).* Pinacolborane (0.63 mL, 4.36 mmol, 2.0 equiv) was added to a solution of **16** (1.28 g, 2.18 mmol) in THF (11 mL, 0.2 M) at −78 °C under Ar. After the mixture was warmed to −40 °C over 1 h, MeOH (11 mL) was added. The mixture was allowed to stir at 0 °C until the evolution of gas ceased. After K_2CO_3 (1.5 g, 10.9 mmol, 5.0 equiv) was added to the mixture, the reaction mixture was stirred for 3 h at rt and then quenched with aq. NH_4Cl at 0 °C. The aqueous layer was extracted three times with AcOEt. The combined organic layers were dried over Na_2SO_4, filtered through a plug of cotton, and concentrated. The crude product was purified by flash column chromatography (CHROMATOREX-NH, hexane/AcOEt = 3/1 to 1/1) to give **18** (927 mg, 78%, dr = 3.7:1; estimated from the ^{1}H NMR spectrum) as an amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.36 (ddd, J = 2.0, 6.0, 12.4 Hz, 1H), 0.43 (ddd, J = 2.4, 6.8, 12.8 Hz, 0.27H), 1.05 (ddd, J = 9.2, 9.2, 13.2 Hz, 0.27H), 1.22 (ddd, J = 7.2, 10.8, 12.4 Hz, 1H), 1.42−1.47 (m, 0.27H), 1.56−1.70 (m, 2 + 0.54H), 2.18−2.26 (m, 1 + 0.27H), 2.22 (s, 0.81H), 2.25 (s, 3H), 2.33−2.40 (m, 0.27H), 2.61 (ddd, J = 2.8, 6.8, 9.2 Hz, 1H), 2.77 (ddd, J = 7.2, 7.2, 10.0 Hz, 0.27H), 2.82 (ddd, J = 8.0, 9.2, 9.2 Hz, 1H), 3.12 (br, 1H), 3.28 (d, J = 13.2 Hz, 0.27H), 3.42−3.47 (m, 2 + 0.54H), 3.58 (d, J = 13.2 Hz, 1H), 3.68 (d, J = 13.2 Hz, 1H), 3.70 (s, 0.81H), 3.76 (s, 3H), 3.77 (d, J = 4.4 Hz, 0.27H), 3.98 (d, J = 12.0 Hz, 1H), 4.08 (d, J = 13.2 Hz, 1H), 4.10 (d, J = 10.4 Hz, 0.27 H), 4.22 (dd, J = 2.0, 12.0 Hz, 1H), 4.24−4.28 (m, 0.27H), 6.80 (d, J = 8.8 Hz, 0.54H), 6.82 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 7.2 Hz, 1H), 7.09 (dd, J = 7.2, 7.6 Hz, 1H), 7.14 (d, J = 7.2 Hz, 0.27H), 7.15 (dd, J = 6.4, 6.8 Hz, 0.27H), 7.22−7.30 (m, 6 + 1.62H), 7.62 (d, J = 9.2 Hz, 2H), 7.63 (d, J = 8.8 Hz, 0.54 H), 7.71 (d, J = 7.6 Hz, 1H), 7.73 (d, J = 7.2 Hz, 0.27H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.9, 25.0, 29.1, 31.3, 37.6, 38.4, 39.0, 43.4, 50.2, 50.9, 51.6, 51.9, 55.4, 55.5, 55.6, 56.7, 59.6, 59.9, 61.4, 63.6, 66.0, 66.1, 67.1, 68.6, 114.1, 117.8, 120.6, 122.1, 124.1, 124.2, 125.2, 125.4, 126.9, 127.0, 128.2, 128.3, 128.4, 128.7, 129.0, 129.1, 129.9, 130.5, 136.6, 139.0, 139.1, 139.2, 139.3, 139.6, 140.4, 163.3, 163.5, 211.2, 211.7; IR (neat): 2930, 2875, 1704, 1594, 1496,

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1457, 1343, 1260, 1153, 1091, 1024 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{31}H_{35}N_2O_5S_1$ $[M + H]^+$: 547.2267, found 547.2263.

*(3aS,4R,6R,6aS,11bR)-4-Acetyl-3-benzyl-7-((4-methoxyphenyl)-sulfonyl)-2,3,3a,4,5,6,6a,7-octahydro-1H-pyrrolo[2,3-d]carbazole-6-carbaldehyde (**19**).* IBX (609 mg, 2.17 mmol, 1.5 equiv) was added to a solution of **18** (794 mg, 1.45 mmol) in DMSO (7.3 mL, 0.2 M) at rt. The mixture was stirred for 1 h under Ar in the dark and then diluted with CH_2Cl_2. After the mixture was cooled to 0 °C, aq. $NaHCO_3$ and solid $Na_2S_2O_3$ were added carefully. The suspension was stirred for an additional ca. 15 min. The separated aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered through a plug of cotton, and concentrated. The crude product was purified by flash column chromatography (SiO_2, hexane/AcOEt = 5/1 to 1.5/1) to give **19** (641 mg, 81%, dr =17:1; estimated from the ^1H NMR spectrum) as an amorphous solid. Spectral data for the major isomer; ^1H NMR (600 MHz, $CDCl_3$) δ: 0.78 (ddd, *J* = 4.8, 7.8, 12.6 Hz, 1H), 1.33 (ddd, *J* = 7.2, 12.0, 13.2 Hz, 1H), 1.64 (ddd, *J* = 4.8, 7.2, 13.9 Hz, 1H), 2.01 (s, 3H), 2.34 (ddd, *J* = 4.8, 10.2, 12.6 Hz, 1H), 2.36 (ddd, *J* = 4.8, 12.0, 12.0 Hz, 1H), 2.55 (ddd, *J* = 7.2, 7.8, 12.0 Hz, 1H), 2.85 (ddd, *J* = 2.4, 7.8, 10.2 Hz, 1H), 2.96 (ddd, *J* = 4.2, 4.2, 4.2 Hz, 1H), 3.19 (d, *J* = 12.0 Hz, 1H), 3.45 (d, *J* = 2.4 Hz, 1H), 3.78 (s, 3H), 3.90 (d, *J* = 12.0 Hz, 1H), 4.22 (d, *J* = 2.4 Hz, 1H), 6.84 (d, *J* = 9.0 Hz, 1H), 6.98 (d, *J* = 7.2 Hz, 1H), 7.04 (dd, *J* = 7.2, 7.8 Hz, 1H), 7.23−7.28 (m, 4H), 7.32 (d, *J* = 7.2 Hz, 2H), 7.65 (d, *J* = 9.0 Hz, 2H), 7.70 (d, *J* = 6.4 Hz, 1H), 9.64 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 18.0, 28.5, 40.2, 43.8, 49.1, 49.8, 52.0, 55.6, 57.1, 63.6, 67.6, 114.2, 116.3, 124.3, 124.8, 127.2, 128.4, 128.8, 129.0, 129.1, 129.2, 134.3, 137.8, 141.4, 163.5, 197.5, 208.2; IR (neat): 2942, 2826, 1703, 1156 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{31}H_{33}N_2O_5S_1$ $[M + H]^+$: 545.2110, found 545.2131.

*(3aS,6R,6aS,11bR)-4-Acetyl-3-benzyl-7-((4-methoxyphenyl)-sulfonyl)-2,3,3a,4,5,6,6a,7-octahydro-1H-pyrrolo[2,3-d]carbazole-6-carboxylic acid (**20**).* $NaClO_2$ (80% purity, 173 mg, 1.53 mmol, 1.3 equiv) was added dropwise to a mixture of **19** (641 mg, 1.18 mmol), $NaH_2PO_4{\cdot}2H_2O$ (552 mg, 3.54 mmol, 3.0 equiv), and 2-methyl-2-butene (0.63 mL, 5.9 mmol, 5.0 equiv) in *t*-BuOH/H_2O (14.8 mL, 2/1, 0.08 M) at 10 °C. After this addition was complete, the mixture was allowed to stir for 1 h at rt. $CHCl_3$ and brine were then added to the solution. The separated aqueous layer was extracted three times with $CHCl_3$. The combined organic layers were dried over Na_2SO_4, filtered through a plug of cotton, and concentrated under reduced pressure to give **20** as a crude product, which could be used in the next step without purification. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.66 (ddd, *J* = 2.8, 7.2, 12.4 Hz, 0.43H), 0.87 (ddd, *J* = 3.6, 7.2, 14.4 Hz, 1H), 1.03 (ddd, *J* = 4.4, 8.4, 12.4 Hz, 0.43H), 1.13 (ddd, *J* = 4.4, 6.0, 14.4 Hz, 1H), 1.26−1.40 (m, 2 + 0.92H), 2.02 (s, 3H), 2.20 (s, 1,29H), 2.22 (d, *J* = 1.6, 7.6 Hz, 0.43H), 2.30 (d, *J* = 1.6, 10.4 Hz, 1H), 2.53 (ddd, *J* = 5.6, 7.2, 11.6 Hz, 1H), 2.58 (ddd, *J* = 4.4, 4.4, 7.6 Hz, 1H), 2.80 (ddd, *J* = 3.2, 11.6, 11.6 Hz, 1H), 2.87 (ddd, *J* = 7.2, 10.0, 10.0 Hz, 0.43H), 3.17 (ddd, *J* = 3.2, 5.6, 11.6 Hz, 1H), 3.28 (br, 1H), 3.39 (ddd, *J* = 3.2, 11.6, 11.6 Hz, 1H), 3.46−3.57 (m, 2H), 3.65 (s, 0.49H), 3.69 (dd, *J* = 5.2, 13.2 Hz, 1H), 3.75 (s, 3H), 3.77 (s, 0.43H), 3.79−3.90 (m, 0.86H), 3.84 (d, *J* = 13.2 Hz, 1H), 4.25 (d, *J* = 13.2 Hz, 1H), 4.30 (d, *J* = 2.4 Hz, 0.43H), 4.38 (d, *J* = 8.8 Hz, 0.43H), 4.45 (d, *J* = 2.4 Hz, 1H), 6.81 (d, *J* = 8.8 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 0.86H), 7.00 (d, *J* = 7.6 Hz, 1H), 7.04 (dd, *J* = 7.2, 7.6 Hz, 1H), 7.13 (dd, *J* = 7.2, 7.6 Hz, 0.43H), 7.16 (d, *J* = 8.0 Hz, 0.43H), 7.21−7.44 (m, 5 + 3.01H), 7.46 (d, *J* = 6.8 Hz, 2H), 7.66 (d, *J* = 8.8 Hz, 1H), *J* = 7.67 (d, *J* = 8.8 Hz, 2H), 7.72 (d, *J* = 8.8 Hz, 0.86H); ^{13}C NMR (100 MHz, $CDCl_3$) [major isomer] δ: 24.0, 28.1, 40.4, 42.6, 45.9, 50.1, 52.3, 55.5, 57.8, 63.3, 66.9, 114.2, 116.3, 123.3, 124.8, 128.2, 128.3, 128.8, 129.0, 129.1, 129.3, 130.0, 141.1, 163.3, 177.3, 207.4; IR (neat): 3007, 2929, 1707, 1593, 1496, 1457, 1353, 1260, 1158, 1091, 1021 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{31}H_{33}N_2O_6S_1$ $[M + H]^+$: 561.2059, found 561.2048.

*Methyl(3aS,6R,6aS,11bR)-4-acetyl-3-benzyl-7-((4-methoxyphenyl)sulfonyl)-2,3,3a,4,5,6,6a,7-octahydro-1H-pyrrolo[2,3-d]-carbazole-6-carboxylate (**21**).* $TMSCHN_2$ (1.2 mL, 2.4 mmol, 2.0 equiv., 2.0 M in Et_2O) was added to a solution of crude **20** (~1.18 mmol) in PhMe/MeOH (11.8 mL, 4/1, 0.1 M) at rt. After the mixture was stirred for 1 h, the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (CHROMATOREX-DIOL, hexane/AcOEt = 6/1 to 2/1) to give **21** (583 mg, 86%, 2 steps, dr =3.2:1; estimated from the ^1H NMR spectrum) as an amorphous solid. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.58 (ddd, *J* = 2.4, 7.2, 12.8 Hz, 0.31H), 0.92 (ddd, *J* = 6.4, 7.2, 13.2 Hz, 1H), 1.09 (ddd, *J* = 7.2, 9.2, 9.2 Hz, 1H), 1.75 (ddd, *J* = 4.4, 8.8, 14.0 Hz, 1H), 1.90 (ddd, *J* = 2.4, 2.4, 12.8 Hz, 0.31H), 2.11 (s, 3H), 2.21 (s, 0.93H), 2.26−2.35 (m, 0.93H), 2.28 (ddd, *J* = 6.4, 9.2, 9.2 Hz, 1H), 2.37 (ddd, *J* = 6.4, 8.4, 14.0 Hz, 1H), 2.49 (dd, *J* = 12.4, 12.4 Hz, 0.31H), 2.58 (ddd, *J* = 4.0, 8.8, 8.8 Hz, 0.31H), 2.74 (ddd, *J* = 7.2, 7.2, 9.2 Hz, 1H), 2.82 (ddd, *J* = 7.6, 9.2, 9.2 Hz, 0.31H), 2.89 (ddd, *J* = 4.0, 6.4, 8.8 Hz, 1H), 2.94 (ddd, *J* = 4.8, 6.8, 8.4 Hz, 1H), 3.22 (d, *J* = 13.2 Hz, 0.31H), 3.40 (d, *J* = 13.6 Hz, 1H), 3.52 (d, *J* = 4.0 Hz, 1H), 3.67 (d, *J* = 13.2 Hz, 0.31H), 3.71 (br, 1H), 3.76 (s, 0.93H), 3.77 (s, 3H), 3.79 (s, 3H), 3.83 (s, 0.93H), 3.97 (d, *J* = 13.6 Hz, 1H), 4.27 (d, *J* = 9.2 Hz, 0.31H), 4.35 (d, *J* = 6.8 Hz, 1H), 6.81 (d, *J* = 8.8 Hz, 0.63H), 6.82 (d, *J* = 8.8 Hz, 2H), 7.00 (d, *J* = 7.6 Hz, 1H), 7.06 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.12 (dd, *J* = 7.6, 7.6 Hz, 0.31H), 7.17 (d, *J* = 7.2 Hz, 0.31H), 7.22−7.31 (m, 6 + 1.86H), 7.66 (d, *J* = 8.8 Hz, 2H), 7.67 (d, *J* = 8.8 Hz, 0.62H), 7.68 (d, *J* = 7.2 Hz, 1H) 7.72 (d, *J* = 8.0 Hz, 0.31H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.1, 22.6, 28.6, 29.1, 29.7, 38.7, 40.7, 44.0, 47.9, 48.4, 49.8, 50.0, 50.9, 52.2, 53.2, 55.3, 55.5, 56.5, 58.7, 59.6, 64.5, 65.6, 67.9, 68.6, 114.0, 114.1, 116.7, 117.6, 121.9, 123.7, 124.7, 125.1, 127.0, 128.2, 128.3, 128.4, 128.5, 129.0, 129.1, 129.9, 130.6, 134.8, 136.3, 138.8, 139.0, 140.3, 140.6, 163.2, 163.3, 173.3, 174.2, 208.9, 209.5; IR (neat): 2949, 1733, 1707, 1594, 1496, 1458, 1354, 1259, 1158, 1092, 1022 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{32}H_{35}N_2O_6S_1$ $[M + H]^+$: 575.2216, found 575.2224.

*Methyl(3aS,6R,6aS,11bR)-4-acetyl-7-((4-methoxyphenyl)-sulfonyl)-2,3,3a,4,5,6,6a,7-octahydro-1H-pyrrolo[2,3-d]carbazole-6-carboxylate (**22**).* $PdCl_2$ (53.2 mg, 0.3 mmol, 30 mol %) was added to a solution of **21** (580 mg, 1.0 mmol) in MeOH (20 mL). The mixture was vigorously stirred under hydrogen gas at ambient pressure and rt. After the mixture was stirred for 21.5 h, an excess amount of NEt_3 was added, and the color of the solution turned from gray to black. After the solid was removed by filtration, the filtrate was concentrated under vacuum. The crude product was purified by flash column chromatography (CHROMATOREX-DIOL, hexane/AcOEt = 2/1 to 1/3) to give **22** (418 mg, 86%, dr =1.4:1; estimated from the ^1H NMR spectrum) as an amorphous solid. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.71 (ddd, *J* = 2.4, 6.8, 13.2 Hz, 0.71H), 1.06 (ddd, *J* = 4.8, 7.6, 12.4 Hz, 1H), 1.23 (ddd, *J* = 10.0, 10.0, 13.2 Hz, 0.71H), 1.34 (ddd, *J* = 8.0, 8.0, 12.4 Hz, 1H), 1.77 (ddd, *J* = 6.0, 10.4, 14.4 Hz, 1H), 1.84 (ddd, *J* = 3.2, 3.2, 12.8 Hz, 0.71H), 1.94 (br, 1 + 0.71H), 2.15 (s, 3H), 2.16 (s, 2.13H), 2.30 (ddd, *J* = 2.0, 6.0, 14.4 Hz, 1H), 2.39 (ddd, *J* = 3.2, 3.2, 12.8 Hz, 0.71H), 2.53 (ddd, *J* = 3.2, 6.0, 13.2 Hz, 0.71H), 2.63 (ddd, *J* = 6.4, 8.0, 10.0 Hz, 1H), 2.86−2.93 (m, 2 + 1.42H), 3.06 (ddd, *J* = 6.0, 7.6, 7.6 Hz, 1H), 3.54 (d, *J* = 8.0 Hz, 1H), 3.78 (ddd, *J* = 2.4, 6.4, 6.4 Hz, 0.71H), 3.81 (s, 3 + 2.13H), 3.82 (s, 3 + 2.13H), 3.98 (d, *J* = 2.0 Hz, 0.71H), 4.15 (d, *J* = 6.0 Hz, 0.71H), 4.32 (d, *J* = 4.4 Hz, 1H), 6.86 (d, *J* = 9.2 Hz, 2 + 1.42H), 7.01 (d, *J* = 7.2 Hz, 1.42H), 7.07 (d, *J* = 8.0 Hz, 1H), 7.08 (dd, *J* = 7.2, 7.6 Hz, 0.71H), 7.26 (dd, *J* = 7.2, 7.6 Hz, 1H), 7.66−7.73 (m, 4 + 2.84H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.2, 23.8, 28.3, 29.6, 40.4, 41.9, 43.1 43.1, 43.4, 48.3, 49.3, 50.0, 52.3, 52.4, 53.6, 54.0, 54.6, 55.6, 58.0, 61.0, 67.6, 68.5, 114.0, 114.1, 117.1, 117.4, 121.8, 123.0, 125.0, 128.5, 128.8, 129.0, 129.3, 129.4, 130.8, 135.0, 138.3, 139.8, 140.5, 163.3, 163.3, 166.2, 173.7, 173.9, 209.3, 209.6; IR (neat): 2949, 2859, 1732, 1707, 1594, 1353, 1259, 1157, 1092, 1022, 834 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{25}H_{29}N_2O_6S_1$ $[M + H]^+$: 485.1746, found 485.1731.

*Methyl(3aS,6R,6aS,11bR)-4-acetyl-3-(3-iodopropyl)-7-((4-methoxyphenyl)sulfonyl)-2,3,3a,4,5,6,6a,7-octahydro-1H-pyrrolo-[2,3-d]carbazole-6-carboxylate (**23**).* 1,3-Diiodopropane (19 μL, 0.17 mmol, 3.0 equiv) was added to a mixture of **22** (26.6 mg, 0.055 mmol) and $NaHCO_3$ (27.7 mg, 0.33 mmol, 6.0 equiv) in DMF (0.55 mL). After being stirred for 6 h at 35 °C, the reaction was quenched by the successive addition of AcOEt and water. The separated organic layer was washed twice with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash column chromatography (CHROMATOREX-DIOL, hexane/AcOEt

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J. Org. Chem. 2015, 80, 8859−8867

= 5/1 to 3/1) to give **23** (19.4 mg, 55%, dr =1.3:1; estimated from the ^{1}H NMR spectrum) as an amorphous solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 0.74 (ddd, J = 1.8, 7.8, 13.2 Hz, 0.79H), 0.88 (ddd, J = 7.8, 7.8, 12.0 Hz, 0.79H), 0.94 (ddd, J = 5.4, 6.6, 12.0 Hz, 1H), 1.19 (ddd, J = 6.6, 9.0, 13.2 Hz, 1H), 1.25−1.30 (m, 1 + 0.79H), 1.72 (ddd, J = 4.8, 7.8, 12.6 Hz, 1H), 1.83−1.96 (m, 2 + 2.37H), 2.09 (s, 3H), 2.22 (s, 2.37H), 2.23−2.40 (m, 4 + 3.16H), 2.58 (ddd, J = 4.8, 9.0, 12.0 Hz, 0.79H), 2.77 (ddd, J = 7.8, 7.8, 12.0 Hz, 0.79H), 2.81−2.83 (m, 1H), 2.89−2.94 (m, 2H), 3.02 (ddd, J = 9.0, 9.0, 9.0 Hz, 0.79H), 3.10 (ddd, J = 7.8, 9.6, 9.6 Hz, 0.79H), 3.17−3.24 (m, 2 + 0.79H), 3.40 (d, J = 3.0 Hz, 1H), 3.56 (s, 0.79H), 3.80 (s, 3 + 2.37H), 3.81 (s, 3H), 3.82 (s, 2.37H), 4.24 (d, J = 9.0 Hz, 0.79H), 4.32 (d, J = 6.6 Hz, 1H), 6.87 (d, J = 9.0 Hz, 2H), 6.88 (d, J = 7.8 Hz, 1.58H), 7.02 (d, J = 6.6 Hz, 1H), 7.05 (dd, J = 7.2, 7.8 Hz, 1H), 7.11−7.12 (m, 1.58H), 7.23 (dd, J = 7.2, 8.4 Hz, 1H), 7.27−7.29 (m, 1.58H), 7.66 (d, J = 8.4 Hz, 1H), 7.69 (d, J = 9.0 Hz, 2H), 7.71 (d, J = 7.8 Hz, 1.58H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 3.6, 4.7, 21.6, 22.4, 28.7, 28.9, 32.1, 32.8, 38.6, 40.8, 44.1, 47.8, 48.3, 49.5, 49.9, 50.5, 52.3, 52.9, 54.3, 55.4, 55.6, 56.3, 64.4, 65.6, 67.9, 68.3, 114.1, 114.2, 116.6, 117.5, 121.9, 123.7, 124.7, 125.1, 128.6, 129.1, 129.2, 129.9, 130.6, 134.8, 136.0, 140.3, 140.8, 163.3, 173.2, 174.1, 208.7, 209.3; IR (neat): 2949, 1733, 1594, 1496, 1458, 1354, 1259, 1158, 1092, 1021, 835 cm^{-1}; HRMS (ESI): m/z calcd for $C_{28}H_{34}I_1N_2O_6S_1$ [M + H]$^+$: 653.1182, found 653.1182.

*Methyl(3aR,3a^{1}R,5R,5aS,10bR)-3a-acetyl-6-((4-methoxyphenyl)-sulfonyl)-2,3,3a,3a^1,4,5,5a,6,11,12-decahydro-1H-indolizino[8,1-cd]carbazole-5-carboxylate (**24**) from **22**.* 1,3-Diiodopropane (14.2 μL, 0.12 mmol, 3.0 equiv) was added to a mixture of **22** (20 mg, 0.041 mmol, 90% ee) and iPr$_2$NEt (43 μL, 0.25 mmol, 6.0 equiv) in MeCN (0.41 mL, 0.1 M). The mixture was heated to 45 °C for 48 h. After all **22** was consumed as monitored by TLC (CH_2Cl_2/MeOH = 20/1), t-BuOH (0.41 mL) and t-BuONa (19.7 mg, 0.2 mmol, 5.0 equiv) were added to the mixture successively at 0 °C. After being stirred for 1 h at 0 °C, the reaction was quenched by the successive addition of AcOEt and aq. NH_4Cl. The aqueous layer was extracted three times with AcOEt. The combined organic layers were dried over Na_2SO_4, filtered through a plug of cotton, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, hexane/AcOEt = 1/1 to 1/2) to give **24** (12.1 mg, 56%, a single diastereomer) as an amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.91−0.99 (m, 2H), 1.37 (ddd, J = 4.2, 7.8, 7.8 Hz, 1H), 1.55−1.64 (m, 2H), 1.77−1.82 (m, 2H), 1.98 (s, 3H), 2.00 (ddd, J = 2.4, 11.4, 11.4 Hz, 1H), 2.12 (ddd, J = 9.0, 9.0, 9.0 Hz, 1H), 2.48 (ddd, J = 2.4, 10.2, 12.6 Hz, 1H), 2.58 (dd, J = 12.6, 13.8 Hz, 1H), 2.88 (ddd, J = 3.6, 9.0, 9.0 Hz, 1H), 2.99−3.01 (m, 1H), 3.05 (s, 1H), 3.80 (s, 3H), 3.82 (s, 3H), 4.19 (d, J = 9.6 Hz, 1H), 6.83 (d, J = 9.0 Hz, 2H), 7.07 (d, J = 7.2, 7.8 Hz, 1H), 7.20 (dd, J = 7.2, 7.8 Hz, 1H), 7.21 (d, J = 7.2 Hz, 1H), 7.61 (d, J = 7.2 Hz, 1H), 7.65 (d, J = 9.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 20.9, 24.9, 27.2, 33.6, 40.4, 46.4, 50.7, 52.2, 52.3, 52.7, 54.5, 55.5, 64.4, 70.0, 114.0, 116.8 124.5, 124.6, 128.2, 129.1, 131.0, 136.4, 139.5, 163.1, 174.0, 209.7; IR (neat): 2942, 1742, 1693, 1601, 1354, 1259, 1159 cm^{-1}; HRMS (ESI): m/z calcd for $C_{28}H_{33}N_2O_6S_1$ [M + H]$^+$: 525.2059, found 525.2077; $[\alpha]_D^{22}$ − 81.7 (c 0.63, $CHCl_3$).

*Methyl(3aR,3a^{1}R,5R,5aS,10bS)-3a-acetyl-2,3,3a,3a^1,4,5,5a,6,11,12-decahydro-1H-indolizino[8,1-cd]-carbazole-5-carboxylate (**25**).* $KPPh_2$ (1.5 mL, 0.75 mmol, 3.0 equiv., 0.5 M in THF) was added to a THF (5.0 mL) solution of **24** (131 mg, 0.25 mmol, 94% ee) at −40 °C, and the mixture was gradually warmed to 0 °C over 1 h. The reaction was then quenched by HCl in MeOH (1.25 M, 1.2 mL, 1.5 mmol, 6.0 equiv). After being concentrated under reduced pressure, the mixture was dissolved in PhMe/MeOH (5.0 mL, 4/1, 0.1 M) at rt. $TMSCHN_2$ (0.6 mL, 1.2 mmol, 4.8 equiv., 2.0 M in ether) was added to the mixture, which was then stirred for 10 min. After the mixture was concentrated under reduced pressure, the residue was purified by flash column chromatography (CHROMATOREX-DIOL, hexane/AcOEt = 6/1 to 3/1) to afford **25** (40.7 mg, 46%) as an amorphous solid, and **24** (8.8 mg, 7%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.49−1.64 (m, 4H), 1.77−1.84 (m, 1H), 1.99 (dd, J = 3.6, 13.2 Hz, 1H), 2.09 (s, 3H), 2.13 (dd, J = 4.0, 11.6, 11.6 Hz, 1H), 2.25 (dd, J = 13.2, 13.2 Hz, 1H), 2.30−2.48 (m, 3H), 3.09 (s, 1H), 3.59 (d, J = 10.0 Hz, 1H), 3.74 (s, 3H), 4.41 (br, 1H), 6.57 (d, J = 7.2 Hz, 1H), 6.71 (dd, J = 7.2, 7.2 Hz, 1H), 6.99 (dd, J = 7.2, 8.0 Hz, 1H), 7.10 (d, J = 7.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 21.2, 25.3, 26.0, 33.3, 37.9, 44.4, 51.6, 52.0, 52.3, 52.9, 54.8, 64.7, 66.0, 110.1, 118.7, 123.8, 128.0, 131.4, 149.1, 175.2, 210.2; IR (neat): 3369, 2928, 2791, 1719, 1688, 1592 cm^{-1}; HRMS (ESI): m/z calcd for $C_{21}H_{27}N_2O_3$ [M + H]$^+$: 355.2022, found 355.2016; $[\alpha]_D^{28}$ − 42.4 (c 0.46, $CHCl_3$).

*Methyl(3aR,3a^{1}R,10bR)-3a-acetyl-2,3,3a,3a^1,4,6,11,12-octahydro-1H-indolizino[8,1-cd]carbazole-5-carboxylate ((−)-minovincine, (**1**)).* DDQ (3.4 mg, 0.014 mmol, 1.6 equiv) was added to a solution of **25** (3.2 mg, 0.009 mmol, 94% ee) in PhMe (0.2 mL, 0.05 M) at 0 °C. After being stirred for 1 h at rt, the mixture was quenched with an excess amount of NEt_3 and filtered successively through Celite and a short pad of silica gel. The column was washed with AcOEt. After the combined organic solutions were concentrated under reduced pressure, the residue was purified by flash column chromatography (SiO_2, hexane/AcOEt = 6/1 to 3/1) to afford **1** (1.3 mg, 41%) as an amorphous solid, and **25** (1.1 mg, 34%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.43 (ddd, J = 6.4, 12.8, 12.8 Hz, 1H), 1.63 (ddd, J = 2.4, 2.4, 12.8 Hz, 1H), 1.61−1.65 (m, 1H), 1.76 (dd, J = 4.4, 11.6 Hz, 1H), 1.88 (s, 3H), 1.98 (dd, J = 6.4, 11.6 Hz, 1H), 1.93−2.00 (m, 1H), 2.47 (ddd, J = 2.8, 11.2, 11.2 Hz, 1H), 2.73 (ddd, J = 4.0, 8.0, 11.6 Hz, 1H), 2.80 (dd, J = 2.4, 11.2 Hz, 1H), 2.96 (dd, J = 6.4, 8.0 Hz, 1H), 3.06 (d, J = 11.2 Hz, 1H), 3.13 (dd, J = 6.4, 8.0 Hz, 1H), 3.26 (s, 1H), 3.77 (s, 3H), 6.78 (d, J = 7.2 Hz, 1H), 6.92 (dd, J = 7.2, 7.2 Hz, 1H), 7.12 (dd, J = 7.2, 7.2 Hz, 1H), 7.30 (d, J = 7.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 22.4, 25.1, 25.9, 29.7, 31.1, 45.3, 49.8, 51.1, 51.5, 53.9, 56.2, 68.0, 91.4, 109.4, 120.7, 121.1, 127.2, 138.2, 142.4, 168.3, 212.2; IR (neat): 3400, 2378, 2375, 2230, 2132, 2085, 1956, 826 cm^{-1}; HRMS (ESI): m/z calcd for $C_{21}H_{25}N_2O_3$ [M + H]$^+$: 353.1860, found 353.1868; $[\alpha]_D^{29}$ − 431.4 (c 0.13, EtOH). (Lit.: natural isolate: $[\alpha]_D^{20}$ − 504 ± 5 (c 0.5, EtOH),[9a] MacMillan's synthetic (−)-minovincine: $[\alpha]_D^{23}$ − 418.3 (c 0.49, EtOH).[12]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge via the Internet at The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01393.

NMR spectra and HPLC spectra for obtained compounds. An ORTEP drawing of compound **14** (PDF)
(CIF)

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Notes

The authors declare no competing financial interest.

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