TOTAL SYNTHESIS OF BIOACTIVE INDOLO[3,2-j]PHENANTHRIDINE ALKALOID, CALOTHRIXIN B

Shigeo Tohyama, Tominari Choshi,* Kohji Matsumoto, Akira Yamabuki, Yuhzo Hieda, Junko Nobuhiro, and Satoshi Hibino*

Graduate School of Pharmacy & Pharmaceutical Sciences, and Faculty of Pharmacy & Pharmaceutical Sciences, Fukuyama University, Fukuyama, Hiroshima 729-0292, Japan
E-mail: hibino@fupharm.fukuyama-u.ac.jp, choshi@fupharm.fukuyama-u.ac.jp

This paper is dedicated to Professor Dr. Albert Eschenmoser on occasion of his 85th birthday.

Abstract – The total synthesis of bioactive calothrixin B (2) was completed which two kinds of carbazoles using three approaches. The common strategy was based on an allene-mediated electrocyclic reaction of a 6π-electron system involving one or two indole [b]-bonds for the construction of an appropriate 4-oxygenated 2,3,4-trisubstituted carbazole 28 or a 6-oxygenated 5-methylindolo[2,3-a]carbazole 39, respectively. Oxidation of the methyl group of 28 followed by reduction of the nitro group of 21 afforded the pentacyclic phenol 5, which was oxidized with CAN to give calothrixin B (2). In a biomimetic pathway, the fully protected 5-formylindolo[2,3-a]carbazole 40 with a methoxymethyl group provided calothrixin B (2) through N-methoxymethyl-calothrixin B 43.

INTRODUCTION

The novel and unique natural products calothrixins A (1) and B (2) were isolated and identified in 1999 from Calothrix cyanobacteria by Rickards and co-workers.1 They proposed that calothrixins A (1) and B (2) may be derived biosynthetically from a hypothetical metabolite 3 of the relatively common indolo[2,3-a]carbazole,1 which is closely related to the known 5-cyano-6-methoxyindolo[2,3-a]carbazole (4) isolated from the cyanobacterium Nostoc sphaericum.2-3 These compounds display impressive in vitro cytotoxicity against HeLa cancer cells in the nanomolar range and inhibit the growth of a
chloroquine-resistant strain of the malaria parasite *Plasmodium falciparum*\(^1\-^4,^7\). Calothrixin A (1) also inhibits bacterial RNA polymerase.\(^6\) Recently, calothrixin A (1) and its derivative \(O\)-methylcalothrixin A, and calothrixin B (2) and its derivative \(N\)-methylcalothrixin B were reported to be cytotoxic to cultured CEM leukemia cells, poisoning DNA topoisomerase 1.\(^8\)

![Calothrixins](image)

**Figure 1**

The calothrixins have a unique indolo\([3,2-j]\)phenanthridine framework which, in addition to their remarkable biologic activities, makes them interesting targets for synthetic chemists. Eight synthetic efforts including two biomimetic routes, have been reported over the last decade.\(^10-^20\) We are interested in the synthesis of bioactive condensed heterocyclic compounds including natural products, based on a thermal electrocyclic reaction with either a 6\(\pi\)-electron system or an aza 6\(\pi\)-electron system including an aromatic or heteroaromatic double bond.\(^21-^22\) Preliminary reports of our synthesis of calothrixin B (2) have been published.\(^15,^18\) We report herein the full details of total synthesis of calothrixin B (2) based on an allene-mediated electrocyclic reaction of a 6\(\pi\)-electron system including the indole \([b]\)-bond\(^15,^22\) or two indole \([b]\)-bonds.\(^18,^22\)

**RESULTS AND DISCUTION**

![Scheme](image)

A retrosynthetic route is depicted in Scheme 1. Calothrixin B is obtained from 7-hydroxyindolo\([3,2-j]\)phenanthridine 5 through oxidation. A 7-hydroxyindolo\([3,2-j]\)phenanthridine 5
might be prepared from a 4-oxygenated 2,3,4-trisubstituted carbazole 6, derived from disconnection of the C4a-N5 position of a pentacyclic phenol 5, by thermal electrocyclic reaction of an aza 6π-electron system including carbazole [b]-bond and benzene [a]-bond. We thought that a 4-oxygenated 2,3,4-trisubstituted carbazole 6 is obtained from a 4-oxygenated 2,3,4-trisubstituted carbazole-3-carbaldehyde 7. A 4-oxygenated 2,3,4-trisubstituted carbazole-3-carbaldehyde 7 would be obtained from a 3-alkoxymethylcarbazole 8 through an oxidation step. It was presumed that an important carbazole 8, derived from disconnection of the C2-C3 position of a carbazole 8, would be obtained from a 2-alkenyl-3-propargylindole 9 by an allene-mediated electrocyclic reaction of a 6π-electron system including the indole [b]-bond.\textsuperscript{15,22}

\begin{center}
\textbf{Scheme 2}
\end{center}

To synthesize the 3-iminocarbazole 18, we chose 2-formyl-N-phenylsulfonylindole 10\textsuperscript{23} as a starting material (Scheme 2). The Wittig reaction of 10 with benzyltriphenylphosphorane gave the 2-styrylindole 11 (83%). Sequential treatment of 11 with α,α-dichloromethyl methyl ether in the presence of AlCl\textsubscript{3}\textsuperscript{24} afforded the 2-alkenyl-3-formylindole 12 (59%). Treatment of 12 with lithium ethoxyacetylide prepared

\[ \text{Ph}_3\text{P} = \begin{array}{c} \text{CHO} \\
\text{Ph} \end{array} \quad \text{Ph}_3\text{PCH}_2\text{PhBr} \\
n-\text{BuLi} \quad \text{THF} \quad \text{rt, 14 h} \quad 83\% \\
\text{MeOCHCl}_2 \\
\text{AlCl}_3 \quad \text{CH}_2\text{Cl}_2 \quad -78 \degree \text{C}, 3 \text{ h} \quad 59\% \]

\[ \text{HNET}_2, n-\text{BuLi, CH}_2\text{ClICH(OEt)}_2 \quad \text{THF} \quad 0 \degree \text{C to rt, 1 h} \quad 85\% \]

\[ \text{H}_2\text{O, CH}_2\text{OH, THF} \quad 90 \degree \text{C, 1 h} \quad 45\% \]

\[ \text{NH}_2\text{OMe} \cdot \text{HCl} \quad \text{AcONa, EtOH} \quad 80 \degree \text{C}, 12 \text{ h, 97\%} \]

\[ \text{or} \quad \text{NH}_2\text{CH(Me)}_2, \text{DMF} \quad \text{rt, 30 min, 93\%} \]

\[ \text{17} \quad \text{18a: R}^1=R^2=\text{H, R}^3=\text{OMe} \quad \text{18c: R}^1=R^2=\text{H, R}^3=\text{CH(Me)}_2 \]

\[ \text{Ac}_2\text{O} \quad \text{DMAP} \quad \text{pyridine} \quad \text{rt, 2 h} \quad 90\% \]

\[ \text{18b} \]

\[ \text{18b} \]

\[ \text{18b} \]
from chloroacetaldehyde diethyl acetal according to Raucher’s method\textsuperscript{25} gave the 3-propargyl indole 13 (85%), which was protected with chloromethyl methyl ether (MOMCl) and \(N,N\)-diisopropylethylamine to produce the \(O\)-MOM ether 14 (86%) corresponding to 9. The propargyl ether 14 was subjected to an allene-mediated electrocyclic reaction in the presence of \(t\)-BuOK in \(t\)-BuOH and THF at 90 °C \textsuperscript{22,26} to yield the desired 3-ethoxymethylcarbazole 16 along with elimination of the \(N\)-phenylsulfonyl group\textsuperscript{22} in somewhat low yield (45%). Subsequent oxidation of 16 with DDQ in toluene gave the 3-formyl-4-hydroxycarbazole 17 (67%), which is a presumed compound 7. Treatment of 17 with \(O\)-methylhydroxylamine in EtOH or with isopropylamine in DMF gave the \(O\)-methyloxime 18a (97%) and the iminocarbazole 18c (93%), respectively. Subsequently, acetylation of 18a with Ac\(_2\)O and DMAP in pyridine yielded the \(N,O\)-diacetylcarbazole 18b (90%).

Table 1. Synthetic Study of Indolo[3,2-\(\gamma\)]phenanthridine by a Thermal or Microwave-assisted Electrocyclic Reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting Material</th>
<th>Solvent</th>
<th>Microwave*</th>
<th>Temp (°C)</th>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(R^1=R^2=H, R^3=\text{OMe})</td>
<td>1,2-dichlorobenzene</td>
<td>-</td>
<td>180</td>
<td>4(h)</td>
<td>N.D.** -</td>
</tr>
<tr>
<td>2</td>
<td>(R^1=R^2=H, R^3=\text{OMe})</td>
<td>toluene/sealed tube</td>
<td>-</td>
<td>140</td>
<td>12(h)</td>
<td>N.D. -</td>
</tr>
<tr>
<td>3</td>
<td>(R^1=R^2=H, R^3=\text{OMe})</td>
<td>decalin</td>
<td>-</td>
<td>210</td>
<td>5(h)</td>
<td>N.D. -</td>
</tr>
<tr>
<td>4</td>
<td>(R^1=R^2=H, R^3=\text{OMe})</td>
<td>toluene</td>
<td>+</td>
<td>150</td>
<td>10</td>
<td>N.D. -</td>
</tr>
<tr>
<td>5</td>
<td>(R^1=R^2=H, R^3=\text{OMe})</td>
<td>DMF</td>
<td>+</td>
<td>210</td>
<td>5</td>
<td>N.D. 33</td>
</tr>
<tr>
<td>6</td>
<td>(R^1=R^2=H, R^3=\text{OMe})</td>
<td>nitrobenzene</td>
<td>+</td>
<td>210</td>
<td>10</td>
<td>N.D. -</td>
</tr>
<tr>
<td>7</td>
<td>(R^1=R^2=\text{Ac}, R^3=\text{OMe})</td>
<td>1,2-dichlorobenzene</td>
<td>+</td>
<td>180</td>
<td>10</td>
<td>N.D. -</td>
</tr>
<tr>
<td>8</td>
<td>(R^1=R^2=\text{Ac}, R^3=\text{OMe})</td>
<td>DMF</td>
<td>+</td>
<td>210</td>
<td>60</td>
<td>N.D. 19</td>
</tr>
<tr>
<td>9</td>
<td>(R^1=R^2=H, R^3=\text{CH(Me)}_2)</td>
<td>DMF</td>
<td>+</td>
<td>210</td>
<td>45</td>
<td>N.D. -</td>
</tr>
</tbody>
</table>

*Microwave: Discover CEM Corp. **N.D.: not detected

Next, an electrocyclic reaction of the 3-iminocarbazole 18 was investigated to afford a desired indolo[3,2-\(\gamma\)]phenanthridine 19 (Table 1). We examined the effect of reaction temperature (entries 1-3), and then performed an electrocyclic reaction of the oxime ether 18a in each solvent at 140-210 °C. However, the cyclization reaction did not proceed and the starting material was recovered. Furthermore,
this reaction of 18a was performed under microwave irradiation using the same substrate (entries 4-6). An indolo[3,2-j]phenanthridine 19 was not obtained, and the starting material was only recovered. As depicted in entry 5, the carbazole-3-carbonitrile 20 was obtained as a by-product in low yield. Although we then attempted the same cyclization using the oxime ether 18b (entries 7,8) and imine 18c (entry 9), similar results were obtained without 19, respectively. Based on this result, we turned to the next route for the synthesis of calothrixin B.

Scheme 3

An alternative retrosynthetic route is depicted in Scheme 3. A 4-oxygenated 2,3,4-trisubstituted carbazole 21, a derivative having a nitro group of 17, was a key compound in Scheme 3. Therefore, the carbazole 21, derived from a disconnection of the N5-C6 position of a pentacyclic phenol 5, is prepared from a 4-oxygenated 2,3,4-trisubstituted carbazole 22 through an oxidation step. It was presumed that an important carbazole 22 would be obtained from a 2-alkenyl-3-propargylindole 23, derived from disconnection of the C2-C3 position of the carbazole 22, by an allene-mediated electrocyclic reaction of a 6π-electron system including the indole [b]-bond. To synthesize 23, the Wittig reaction of 10 with 2-nitrobenzyltriphenylphosphorane gave the 2-(2-styryl)indole 24 (96%) (Scheme 4). Sequential treatment of 24 with α,α-dichloromethyl methyl ether in the presence of AlCl₃ afforded the 2-alkenyl-3-formylindole 25 (96%). The Grignard reaction of 25 with ethynylmagnesium bromide yielded the propargyl alcohol 26, which was protected with chloromethyl methyl ether (MOMCl) and N,N-diisopropylethylamine to produce the propargyl ether 27 corresponding to 23 in this route (86% from 25). The propargyl ether 27 was subjected to an allene-mediated electrocyclic reaction in the presence of t-BuOK in t-BuOH and THF at 90 °C to yield the desired 4-oxygenated 2,3,4-trisubstituted carbazole 28 along with elimination of the N-phenylsulfonyl group in somewhat low yield (29%). Subsequent oxidation of 28 with DDQ in the presence of lithium perchlorate in CH₂Cl₂ gave the 3-formyl-4-hydroxycarbazole 21 (70%), which is a presumed compound 21 in Scheme 3. Reduction of the nitro group of 21 with 10% Pd-C and H₂, followed by the
intramolecular condensation afforded the pentacyclic indolo[3,2-\(j\)]phenanthridine 5, which was oxidized with cerium ammonium nitrate (CAN) in an aqueous MeCN to provide calothrixin B (2) (67% yield from 21). The physical and spectroscopic data of synthetic 2 were identical with those of natural calothrixin B (2). The total synthesis of calothrixin B (2) based on the retrosynthetic route (Scheme 3) was completed with a 10.7% overall yield.

Scheme 4

Scheme 5
In a biomimetic route (Scheme 5), disconnection of the N5-C6 bond will produce a carbazole-1,4-quinone 29, which is recycled to an iminoquinone type of indolocarbazole 30. An imino-quinone 30 is easily reduced to an indolo[2,3-α]carbazole 3, which is a hypothetical metabolite, proposed by the Rickards group.1 We envisioned that an important metabolite, 5-formyl-6-hydroxyindolo[2,3-α]carbazole 3 or its derivative 31 might be obtained from a propargyl ether 32 through an allene-mediated electrocyclic reaction of the 6π-electron system including two [b]-bonds of indoles.

![Scheme 6](image-url)

We initially attempted the synthesis of the indolo[2,3-α]carbazole 39 from the propargyl ether 38 using an allene-mediated electrocyclic reaction as a key step (Scheme 6). We selected 2-bromoindole-3-carbaldehyde 33 as the starting material. A Suzuki-Miyaura cross-coupling reaction20 of 33 with the indole-2-boronic acids 34a,b30 gave the bisindoles 35a (99%) and 35b (86%), respectively. Protection of the nitrogen atom of 35a,b with MOMCl and NaH afforded the N-MOM-bisindole 36a,b (73% and 98%). A subsequent Grignard reaction of 36a,b with ethynylmagnesium bromide yielded the propargyl alcohols 37a,b (70% and 70%), which were treated with MOMCl and N,N-diisopropylethylamine to protect the hydroxyl groups of 37a,b. However, propargyl ethers were not obtained. Therefore, cleavage of the N-BOC group in 35a with TFA (96%), followed by protection of the nitrogen atom of the bisindole 35c with MOMCl and NaH afforded the N,N'-bis(methoxymethyl)bisindole 36c (86%). A subsequent Grignard reaction of 36c with ethynylmagnesium bromide yielded the propargyl alcohol 37c (93%), which was protected with MOMCl
and N,N-diisopropylethylamine to produce the propargyl ether 38 (93%). 38 was subjected to an allene-mediated electrocyclic reaction in the presence of t-BuOK in t-BuOH and THF at 90 °C\textsuperscript{22,26} to yield the desired 6-oxygenated 5-methylindolo[2,3-\textit{a}]carbazole 39 (93%).

![Scheme 7](image)

Sequential treatment of the fully protected 39 with DDQ in DMF gave the 5-formylindolo[2,3-\textit{a}]carbazole 40 (74%). This compound was equivalent to the hypothetical metabolite 3. Our attempts to remove the protecting groups of 40 to convert it to a metabolite 3 were unsuccessful. For conversion to a quinone-imine like compound 41, the fully protected indolo[2,3-\textit{a}]carbazole 40 was directly treated with CAN to give the N-MOM-calothrixin B 43 (40%) without detection of an imino-quinone 41 and/or an amino-aldehyde 42. The 5-formylindolo[2,3-\textit{a}]carbazole 3 was synthesized from indigo by the Moody group.\textsuperscript{19,20} Despite many attempts, however, they were unable to achieve oxidation of the non-protected indolo[2,3-\textit{a}]carbazole 3 to obtain the pentacyclic calothrixin B (2). They then used our fully protected indolo[2,3-\textit{a}]carbazole 40 to complete the total synthesis.\textsuperscript{19,20} This result shows that an imino-quinone 41 was formed by the oxidation, and then immediate hydrolysis of an imino group in 41 followed by intramolecular condensation occurred to give the N-MOM-indolo[3,2-\textit{f}]phenanthridine ring system 43. Finally, cleavage of the N-MOM group using Kelly’s method\textsuperscript{10} was performed to yield calothrixin B (2). The total yield of the biomimetic route was 12.6%. The physical and spectroscopic data of N-MOM-calothrixin B 43 were identical with those of Kelly’s synthetic compound 43. Furthermore, the synthetic calothrixin B (2) was similar to the former synthetic calothrixin B (2)\textsuperscript{15} and natural calothrixin B (2)\textsuperscript{1} in all respects.

**CONCLUSIONS**

We investigated the synthesis of calothrixin B (2) by three routes. Construction of the appropriate
4-oxygenated 2,3,4-trisubstitute carbazole ring 21 via 22, derived from cleavage of the N5-C6 bond in the pentacyclic calothrixin framework 5, was achieved by an allene-mediated electrocyclic reaction involving the indole [b]-bond. Reduction of the nitro group of 21 provided the 7-hydroxyindolo[3,2-f]phenanthridine 5, which was converted to calothrixin B (2) (Scheme 4). In addition, the construction of the fully protected 5-formylindolo[2,3-a]carbazole 40, derived from cleavage of the N5-C6 bond followed by cyclization and reduction in the biomimetic route (Scheme 5), was also previously established by an allene-mediated electrocyclic reaction involving the two indole [b]-bonds. In the biomimetic pathway, the fully protected 5-formylindolo[2,3-a]carbazole 40 with a methoxymethyl group fortunately produced calothrixin B (2) through the N-methoxymethyl-calothrixin B 43. The conversion of calothrixin B (2) to calothrixin A (1) was performed by Kelly’s group (Scheme 6). Thus, the total synthesis of calothrixin B (2) was completed in two ways with a common key reaction. This latter total synthesis indicates that calothrixin B (2) was formed naturally using Rickards’s protocol. Furthermore, a new synthetic pathway to a naturally occurring indolo[2,3-a]carbazole alkaloid is provided by this biomimetic route.

**EXPERIMENTAL**

**General.** All non-aqueous reactions were carried out under a positive atmosphere of argon in dried glassware unless otherwise noted. Solvents were dried and distilled according to standard protocols. Analytical thin-layer chromatography was performed with Silica gel 60PF254 (Merck). Silica gel column chromatography was performed with Silica gel 60 (70-230 mesh, Merck). All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (1H-NMR) spectra were recorded on a JEOL AL-300 at 300 MHz. Chemical shifts are reported relative to Me4Si (δ 0.00). Multiplicity is indicated by one or more of the following: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet); br (broad). Carbon nuclear magnetic resonance (13C-NMR) spectra were recorded on a JEOL AL-300 at 75 MHz. Chemical shifts are reported relative to CDCl3 (δ 77.0) and DMSO-d6 (δ 39.7). Infrared spectra were recorded with the ATR method using a Shimadzu FTIR-8000 spectrophotometer and Technologies DuraScop. Low and High resolution mass spectra were recorded on JEOL JMS-700 spectrometers by a direct inlet system.

**N-(Phenylsulfonyl)-2-styrylindole (11).** n-BuLi (2.46 mol/L in hexane, 1.06 mL, 2.63 mmol) was added to a stirred mixture of benzyltriphenylphosphonium bromide (1.02 g, 2.63 mmol) in THF (40 mL) under cooling with ice-water, and then the mixture was stirred at rt for 1 h. A solution of the 2-formylindole 10 (500 mg, 1.75 mmol) in THF (15 mL) was added to this ice-cooled mixture, which was stirred at rt for 14 h. The mixture was quenched with an aqueous NH4Cl (saturated) solution and extracted with EtOAc. The
EtOAc layer was washed with brine, dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 20 g) using EtOAc-hexane (1:19, v/v) as an eluent to give the oily styrylindole 11 (520 mg, 83%). IR (ATR) v: 1369, 1173 cm$^{-1}$; $^1$H-NMR (CDCl$_3$) $\delta$: 6.44 (1H, s), 6.71 (1H, d, $J$=13 Hz), 6.95-7.52 (9H, m), 7.57 (2H, d, $J$=7 Hz), 7.74 (2H, d, $J$=7 Hz), 8.23 (1H, d, $J$=8 Hz), 8.29 (1H, d, $J$=8 Hz); MS m/z: 359 (M$^+$); HR-MS (EI) m/z: 359.0986 (M$^+$), calcd for C$_{22}$H$_{17}$NO$_2$S: 359.0980.

$N$-(Phenylsulfonyl)-2-styrylindole-3-carbaldehyde (12). $\alpha,\alpha$-Dichloromethyl methyl ether (0.13 mL, 1.39 mmol) was added to a mixture of the styrylindole 11 (100 mg, 0.278 mmol) and AlCl$_3$ (185 mg, 1.39 mmol) in CH$_2$Cl$_2$ (10 mL) at -78 °C. After being stirred at the same temperature for 3 h, the reaction mixture was poured into ice-water and extracted with CH$_2$Cl$_2$. The CH$_2$Cl$_2$ layer was washed with brine, dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 5 g) using EtOAc-hexane (1:19, v/v) as an eluent to give the 3-formylindole 12 (64 mg, 59%), mp 172-176 °C (EtOAc). IR (ATR) v: 1658, 1385, 1176 cm$^{-1}$; $^1$H-NMR (CDCl$_3$) $\delta$: 6.80 (1H, d, $J$=16 Hz), 7.34-7.56 (8H, m), 7.62 (2H, d, $J$=8 Hz), 7.75 (1H, d, $J$=16 Hz), 7.78 (2H, d, $J$=8 Hz), 8.27 (1H, d, $J$=8 Hz), 8.34 (1H, d, $J$=8 Hz), 10.03 (1H, s); MS m/z: 387 (M$^+$); HR-MS (EI) m/z: 387.0947 (M$^+$), calcd for C$_{23}$H$_{17}$NO$_3$S: 387.0929.

3-(3-Ethoxy-1-hydroxyprop-2-yn-1-yl)-$N$-(phenylsulfonyl)-2-styrylindole (13). To a solution of Et$_2$NH (2.44 mL, 23.5 mmol) in THF (40 mL) was added n-BuLi (2.46 mol/L in hexane, 8.48 mL, 20.8 mmol) under cooling with ice-water. After being stirred at the same temperature for 10 min, chloroacetalddehyde diethyl acetal (1.01 mL, 6.73 mmol) was added to the reaction mixture at the same temperature, which was then stirred for 1 h. A solution of 3-formylindole 12 (521 mg, 1.35 mmol) in THF (20 mL) was added to a solution of lithium ethoxyacetylide in THF under cooling with ice-water. After being stirred at the room temperature for 1 h, the reaction mixture was quenched with an aqueous NH$_4$Cl (saturated) solution, and then extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 15 g) using EtOAc–hexane (1:9, v/v) as an eluent to give the oily propargyl alcohol 13 (523 mg, 85%). IR (ATR) v: 3529, 2264, 1373, 1173 cm$^{-1}$; $^1$H-NMR (CDCl$_3$) $\delta$: 3.99 (2H, q , $J$=7 Hz), 5.70 (1H, s), 6.68 (1H, d, $J$=16 Hz), 7.19-7.45 (9H, m), 7.51 (2H, d, $J$=7 Hz), 7.66 (2H, d, $J$=7 Hz), 7.97 (1H, d, $J$=8 Hz), 8.18 (1H, d, $J$=8 Hz); MS m/z: 457 (M$^+$); HR-MS (EI) m/z: 457.1355 (M$^+$), calcd for C$_{27}$H$_{23}$NO$_4$S: 457.1348.

3-[3-Ethoxy-1-(methoxymethyloxy)prop-2-yn-1-yl]-$N$-(phenylsulfonyl)-2-styrylindole (14). A solution of the propargyl alcohol 13 (496 mg, 1.08 mmol), MOMCl (0.49 mL, 6.50 mmol) and i-Pr$_2$NET (1.51 mL, 8.67 mmol) in CH$_2$Cl$_2$ (20 mL) was heated at 50 °C for 12 h. After being cooled to an ambient temperature, the reaction mixture was quenched with water and extracted with CH$_2$Cl$_2$. The CH$_2$Cl$_2$ layer
was washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 15 g) using EtOAc-hexane (1:9, v/v) as an eluent to give the oily MOM ether 14 (469 mg, 86%). IR (ATR) ν: 2260, 1369, 1173 cm⁻¹; ¹H-NMR (CDCl₃) δ: 1.27 (3H, t, J=7 Hz), 3.30 (3H, s), 4.03 (2H, q, J=7 Hz), 4.52 (1H, d, J=7 Hz), 4.92 (1H, d, J=7 Hz), 5.74 (1H, s), 6.78 (1H, d, J=16 Hz), 7.24-7.59 (9H, m), 7.73 (2H, d, J=7 Hz), 7.58 (2H, d, J=7 Hz), 7.94 (1H, d, J=8 Hz), 8.24 (1H, d, J=8 Hz); MS m/z: 501 (M⁺); HR-MS (EI) m/z: 501.1629 (M⁺), calcd for C₂₉H₂₇NO₅S: 501.1610.

4-Hydroxy-2-phenylcarbazole-3-carbaldehyde (17). A mixture of the carbazole 16 (30 mg, 0.083 mmol) and DDQ (42 mg, 0.183 mmol) in toluene (25 mL) was stirred at rt for 12 h. The reaction mixture was filtrated through a Celite pad. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 2 g) using EtOAc-hexane (1:19, v/v) as an eluent to give the 3-formylcarbazole 17 (16 mg, 67%), mp 220-224 °C (MeOH). IR (ATR) ν: 3243, 1608 cm⁻¹; ¹H-NMR (CDCl₃) δ: 6.89 (1H, s), 7.45-7.48 (8H, m), 8.40 (1H, d, J=7 Hz), 8.43 (1H, br s), 9.76 (1H, s), 13.43 (1H, s); MS m/z: 287 (M⁺); HR-MS (EI) m/z: 287.0960 (M⁺), calcd for C₁₉H₁₃NO₂: 287.0946.

4-Hydroxy-3-(methoxyiminomethyl)-2-phenylcarbazole (18a). A mixture of the 3-formylcarbazole 17 (30 mg, 0.105 mmol), MeONH₂・HCl (70 mg, 0.835 mmol) and AcONa (69 mg, 0.835 mmol) in EtOH (5 mL) was heated at 80 °C for 12 h. After being cooled to an ambient temperature, the reaction mixture was concentrated under reduced pressure. The mixture was extracted with EtOAc and water. The EtOAc layer was washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 2 g) using EtOAc-hexane (1:19, v/v) as an eluent to give the oxime ether 18a (32 mg, 97%), mp 175-177 °C (EtOAc-hexane). IR (ATR) ν: 3398 cm⁻¹; ¹H-NMR (CDCl₃) δ: 3.97 (3H, s), 6.89 (1H, s), 7.29-7.46 (8H, m), 8.15 (1H, br s), 8.23 (1H, s), 8.41 (1H, d, J=8 Hz), 11.45 (1H, s); MS m/z: 316 (M⁺); HR-MS (EI) m/z: 316.1205 (M⁺), calcd for C₂₀H₁₆N₂O₂: 316.1212.

N-Acetyl-4-(acetoxy)-3-(methoxyiminomethyl)-2-phenylcarbazole (18b). To a solution of the oxime ether 18a (30 mg, 0.095 mmol), and DMAP (0.56 mg, 4.75 mmol) in pyridine (3 mL) was added Ac₂O (90 mL, 0.948 mmol) and then the solution was stirred at rt for 2 h. The reaction mixture was quenched with water, and extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 2 g) using EtOAc-hexane (1:9, v/v) as an eluent to give the diacetylcarbazole 18b (34 mg, 90%), mp 132-134 °C (MeOH). IR (ATR) ν: 1766, 1697 cm⁻¹; ¹H-NMR (CDCl₃) δ: 2.57 (3H, s), 2.89 (3H, s), 3.96 (3H, s), 7.38-7.54 (7H, m), 7.94 (1H, s), 8.05 (1H, d, J=8 Hz), 8.17 (1H, s) 8.19 (1H, d, J=8 Hz); MS m/z: 400 (M⁺); HR-MS (EI) m/z: 400.1437 (M⁺), calcd for C₂₄H₂₆N₂O₄: 400.1423.

4-Hydroxy-3-(isopropyliminomethyl)-2-phenylcarbazole (18c). To a solution of the 3-formylcarbazole
(30 mg, 0.104 mmol) in DMF (5 mL) was added \( i\text{-PrNH}_2 \) (10 mL, 0.115 mmol) and then the solution was stirred at rt for 30 min. The reaction mixture was quenched with water, and extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na\(_2\)SO\(_4\), and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 2 g) using EtOAc-hexane (3:17, v/v) as an eluent to give the 3-iminocarbazole 18c (32 mg, 93%), mp 218-220 °C (EtOAc-hexane). IR (ATR) \( \nu \): 3375 cm\(^{-1}\); \(^1\)H-NMR (CDCl\(_3\)) \( \delta \): 1.32 (6H, s), 3.55 (1H, m), 6.53 (1H, s), 7.30-7.43 (9H, m), 7.86 (1H, s), 8.28 (1H, br s), 8.51 (1H, br s); MS \( m/z \): 328 (M\(^+\)); HR-MS (EI) \( m/z \): 328.1569 (M\(^+\)), calcd for C\(_{22}\)H\(_{20}\)N\(_2\)O: 328.1576.

2-[2-(2-Nitrophenyl)ethenyl]-N-(phenylsulfonyl)indole (24). \( n\)-BuLi (2.59 mol/L in hexane, 1.01 mL, 2.63 mmol) was added to a stirred mixture of 2-nitrobenzyltriphenylphosphonium bromide (1.14 g, 2.63 mmol) in THF (15 mL) under cooling with ice-water, and then the mixture was stirred at rt for 1 h. A solution of the 2-formylindole 10\(^{23}\) (500 mg, 1.75 mmol) in THF (10 mL) was added to this ice-cooled mixture, which was stirred at the same temperature for 3 h. The mixture was quenched with an aqueous NH\(_4\)Cl (saturated) solution and extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na\(_2\)SO\(_4\), and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 20 g) using EtOAc-hexane (1:9, v/v) as an eluent to give a cis/trans mixture of the 2-styrylindole 24 (681 mg, 96%), mp 122-125 °C (EtOAc-hexane). IR (ATR) \( \nu \): 1516, 1365, 1338, 1170 cm\(^{-1}\); \(^1\)H-NMR (CDCl\(_3\)) \( \delta \): 6.02 (1H, s), 6.67 (1H, d, \( J=7.3 \) Hz), 7.03 (1H, d, \( J=11.7 \) Hz), 7.15-7.22 (4H, m), 7.29-7.38 (2H, m), 7.45-7.50 (2H, m), 7.60 (1H, t, \( J=7.3 \) Hz), 7.87-7.90 (2H, m), 8.08 (1H, d, \( J=8.3 \) Hz), 8.26 (1H, d, \( J=8.3 \) Hz); \(^{13}\)C-NMR (75 MHz) \( \delta \): 110.8, 112.7, 114.8, 121.0, 121.1, 121.5, 123.8, 124.0, 124.4, 124.7, 124.8, 125.2, 125.4, 126.6, 126.7, 127.3, 128.4, 128.8, 129.1, 129.3, 129.4, 129.4, 131.4, 133.1, 133.2, 134.0, 135.5, 136.9, 139.1, 148.1; MS \( m/z \): 404 (M\(^+\)); HR-MS (EI) \( m/z \): 404.0825 (M\(^+\)), calcd for C\(_{22}\)H\(_{16}\)N\(_2\)O\(_4\)S: 404.0831.

2-[2-(2-Nitrophenyl)ethenyl]-N-(phenylsulfonyl)indole-3-carbaldehyde (25). \( \alpha,\alpha\)-Dichloromethyl methyl ether (1 mL, 11.03 mmol) was added to a mixture of the 2-styrylindole 24 (892 mg, 2.21 mmol) and AlCl\(_3\) (1.47 g, 11.03 mmol) in CH\(_2\)Cl\(_2\) (20 mL) at -78 °C. After being stirred at the same temperature for 1 h, the reaction mixture was poured into ice-water and extracted with CH\(_2\)Cl\(_2\). The CH\(_2\)Cl\(_2\) layer was washed with brine, dried over Na\(_2\)SO\(_4\), and concentrated under reduced pressure. The residue was recrystallized from EtOAc-hexane to give the 3-formylindole 25 (915 mg, 96%), mp 201-203 °C (EtOAc-hexane). IR (ATR) \( \nu \): 1670, 1520, 1369, 1342, 1173 cm\(^{-1}\); \(^1\)H-NMR (CDCl\(_3\)) \( \delta \): 7.31-7.46 (5H, m), 7.53-7.61 (2H, m), 7.67 (1H, d, \( J=16.1 \) Hz), 7.73 (1H, t, \( J=8.3 \) Hz), 7.81-7.84 (2H, m), 7.89 (1H, d, \( J=6.6 \) Hz), 8.13 (1H, d, \( J=7.0 \) Hz), 8.22 (1H, d, \( J=8.1 \) Hz), 8.33 (1H, d, \( J=7.3 \) Hz), 10.13 (1H, s); \(^{13}\)C-NMR (75 MHz) \( \delta \): 114.3, 121.0, 121.5, 122.5, 125.1, 125.2, 125.6, 126.6, 126.9, 127.1, 129.2, 129.6, 129.8, 129.9, 131.0, 131.6, 134.0, 134.7, 135.8, 136.3, 137.5, 147.0, 187.0; MS \( m/z \): 432 (M\(^+\)); HR-MS (EI) \( m/z \): 432.0810.
(M⁺), calcd for C_{23}H_{16}N_{2}O_{5}S: 432.0780.

3-(1-Hydroxyprop-2-yn-1-yl)-2-[2-(2-nitrophenyl)ethenyl]-N-(phenylsulfonyl)indole (26). A solution of ethynylmagnesium bromide (0.5 M in THF, 14.7 mL, 7.35 mmol) was added to a stirred solution of the 3-formylindole 25 (1.06 g, 2.45 mmol) in THF (40 mL) under cooling with ice-water. After being stirred at the same temperature for 2 h, the reaction mixture was quenched with an aqueous NH₄Cl (saturated) solution, then extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 30 g) using EtOAc–hexane (3:7, v/v) as an eluent to give the propargyl alcohol 26 (1.03 g, 92%), mp 163-165 °C (EtOAc-hexane). IR (ATR) ν: 1520, 1369, 1342, 1173 cm⁻¹, ¹H-NMR (CDCl₃) δ: 2.49 (1H, br s), 2.60 (1H, d, J=7.5 Hz), 5.91 (1H, br s), 7.21-7.40 (4H, m), 7.26 (1H, d, J=16.1 Hz), 7.46-7.55 (2H, m), 7.52 (1H, d, J=16.1 Hz), 7.70-7.78 (3H, m), 7.90 (1H, d, J=7.0 Hz), 7.97-8.11 (2H, m), 8.21 (1H, d, J=8.4 Hz); ¹³C-NMR (75 MHz) δ: 57.4, 74.6, 82.7, 114.8, 121.4, 121.5, 123.0, 124.1, 125.0, 125.8, 126.7, 126.9, 128.0, 129.1, 129.3, 129.4, 132.0, 132.6, 133.9, 134.1, 135.2, 136.5, 137.8, 147.7; MS m/z: 458 (M⁺); HR-MS (EI) m/z: 458.0931 (M⁺), calcd for C_{25}H_{18}N_{2}O_{5}S: 458.0936.

3-[1-(Methoxymethyloxy)prop-2-yn-1-yl]-2-[2-(2-nitrophenyl)ethenyl]-N-(phenylsulfonyl)indole (27). A solution of the propargyl alcohol 26 (1.03 g, 2.25 mmol), MOMCl (1.02 mL, 13.48 mmol) and i-Pr₂NEt (3.1 mL, 17.97 mmol) in CH₂Cl₂ (30 mL) was heated at 50 °C for 12 h. After being cooled to an ambient temperature, the reaction mixture was quenched with water and extracted with CH₂Cl₂. The CH₂Cl₂ layer was washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 30 g) using EtOAc–hexane (3:7, v/v) as an eluent to give the MOM ether 27 (1.05 g, 93%), mp 124-126 °C (Et₂O-hexane). IR (ATR) ν: 1520, 1373, 1342, 1170 cm⁻¹; ¹H-NMR (CDCl₃) δ: 2.54 (1H, d, J=2.2 Hz), 3.25 (3H, s), 4.51 (1H, d, J=7.0 Hz), 4.85 (1H, d, J=7.0 Hz), 5.83 (1H, d, J=2.2 Hz), 7.14-7.61 (8H, m), 7.72 (1H, t, J=7.5 Hz), 7.77-7.80 (2H, m), 7.87-8.03 (2H, m), 8.08 (1H, d, J=8.1 Hz), 8.23 (1H, d, J=8.1 Hz); ¹³C-NMR (75 MHz) δ: 55.7, 60.1, 74.8, 80.7, 93.7, 114.9, 120.1, 121.6, 122.9, 124.2, 124.9, 125.9, 126.8, 129.1, 129.2, 129.5, 131.9, 132.5, 133.8, 134.0, 135.5, 136.6, 137.7, 147.9; MS m/z: 502 (M⁺); HR-MS (EI) m/z: 502.1212 (M⁺), calcd for C_{27}H_{22}N_{2}O_{6}S: 502.1199.

4-(Methoxymethyloxy)-3-methyl-2-(2-nitrophenyl)carbazole (28). A solution of the MOM ether 27 (200 mg, 0.40 mmol) in THF (2 mL) was added to a solution of ℓ-BuOK (223 mg, 1.99 mmol) in ℓ-BuOH (8 mL) and then heated at 90 °C for 30 min. After being cooled to an ambient temperature, the solution was quenched with an aqueous NH₄Cl solution (saturated). The mixture was extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 20 g) using EtOAc-hexane (1:3, v/v) as an eluent to give the oily carbazole 28 (42 mg, 29%). IR (ATR) ν: 1523, 1346 cm⁻¹; ¹H-NMR (CDCl₃) δ:
2.18 (3H, s), 3.63 (3H, s), 5.33 (1H, d, \( J=9.0 \) Hz), 5.35 (1H, d, \( J=9.0 \) Hz), 6.94 (1H, s), 7.23 (1H, d, \( J=6.6 \) Hz), 7.34-7.42 (3H, m), 7.51 (1H, t, \( J=7.7 \) Hz), 7.62 (1H, t, \( J=7.7 \) Hz), 7.99 (1H, d, \( J=7.7 \) Hz), 8.15 (1H, br s), 8.21 (1H, d, \( J=6.6 \) Hz); \(^{13}\)C-NMR (75 MHz) \( \delta \): 13.6, 58.2, 99.5, 106.9, 110.4, 116.4, 119.8, 120.1, 121.4, 122.3, 124.0, 125.8, 128.2, 132.4, 132.5, 136.8, 136.9, 139.0, 139.6, 149.3, 150.9; MS \( m/z \): 362 (M\(^+\)); HR-MS (EI) \( m/z \): 362.1284 (M\(^+\)), calcd for C\(_{21}\)H\(_{18}\)N\(_2\)O\(_4\): 362.1267.

4-Hydroxy-2-(2-nitrophenyl)carbazole-3-carbaldehyde (21). DDQ (35 mg, 0.15 mmol) was added to a solution of the carbazole 28 (28 mg, 0.077 mmol) and LiClO\(_4\) (8 mg, 0.077 mmol) in CH\(_2\)Cl\(_2\)-H\(_2\)O (18:1, 3 mL). The reaction mixture was stirred at rt for 40 h, and filtrated through Celite pad. The filtrate was quenched with water, and extracted with CH\(_2\)Cl\(_2\). The CH\(_2\)Cl\(_2\) layer was washed with brine, dried over Na\(_2\)SO\(_4\), and concentrated. The reactant was used without purification. A solution of the resulting residue, 6 M HCl (0.2 mL), and ethylene glycol (0.2 mL) in THF (3 mL) was heated at 60 °C for 6 h. The mixture was extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na\(_2\)SO\(_4\), and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 1 g) using EtOAc-hexane (1:3, v/v) as an eluent to give the 3-formylcarbazole 21 (18 mg, 70%), mp 254-256 °C (EtOAc-hexane). IR (ATR) \( \nu \): 3293, 1731, 1519, 1353 cm\(^{-1}\); \(^1\)H-NMR (CDCl\(_3\)) \( \delta \): 6.75 (1H, s), 7.34-7.39 (1H, m), 7.63 (1H, t, \( J=7.6 \) Hz), 7.46-7.52 (3H, m), 7.67 (1H, t, \( J=7.6 \) Hz), 8.06 (1H, d, \( J=7.6 \) Hz), 8.40 (1H, d, \( J=7.6 \) Hz), 8.40 (1H, br s), 9.56 (1H, s), 13.20 (1H, s); \(^{13}\)C-NMR (75 MHz) \( \delta \): 104.2, 110.7, 111.3, 111.8, 121.6, 122.7, 123.3, 124.3, 126.1, 129.4, 132.2, 133.1, 133.2, 138.7, 139.7, 144.1, 149.6, 161.5, 194.1; MS \( m/z \): 332 (M\(^+\)); HR-MS (EI) \( m/z \): 332.0703 (M\(^+\)), calcd for C\(_{19}\)H\(_{12}\)N\(_2\)O\(_4\): 332.0797.

Calothrixin B (2). A mixture of the 3-formylcarbazole 21 (5 mg, 0.015 mmol) and 10% Pd-C (20 mg) in EtOH (2 mL) was stirred at rt for 2 h under an H\(_2\) atmosphere. The reaction mixture was filtrated through a Celite pad. The filtrate was concentrated under reduced pressure. The residue was used without purification. A solution of CAN (41 mg, 0.015 mmol) in MeCN-H\(_2\)O (2:1, 1 mL) was added to a solution of the resulting residue in MeCN-H\(_2\)O (2:1, 2 mL) under cooling with ice-water. After being stirred at the same temperature for 1 h, the reaction mixture was quenched with water and extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na\(_2\)SO\(_4\), and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 3 g) using EtOAc-hexane (3:7, v/v) as an eluent to give calothrixin B (2) (3 mg, 67%), mp >300 °C (lit., >300 °C). IR (ATR) \( \nu \): 1731 cm\(^{-1}\); \(^1\)H-NMR (DMSO-\( d_6 \)) \( \delta \): 7.39 (1H, t, \( J=7.7 \) Hz), 7.47 (1H, t, \( J=7.7 \) Hz), 7.63 (1H, d, \( J=7.7 \) Hz), 7.89 (1H, t, \( J=7.7 \) Hz), 7.96 (1H, t, \( J=7.7 \) Hz), 8.17 (1H, d, \( J=7.7 \) Hz), 8.19 (1H, d, \( J=7.7 \) Hz), 9.58 (1H, d, \( J=7.7 \) Hz), 9.63 (1H, s), 13.18 (1H, br s), \(^{13}\)C-NMR (75 MHz, DMSO-\( d_6 \)) \( \delta \): 113.9, 115.4, 122.2, 122.5, 123.3, 124.3, 124.8, 127.1, 127.8, 129.8, 130.2, 131.5, 132.5, 137.9, 138.3, 147.4, 151.1, 180.3, 180.7. MS \( m/z \): 298 (M\(^+\))}. HR-MS (EI) \( m/z \): 298.0733 (M\(^+\)), calcd for C\(_{19}\)H\(_{10}\)N\(_2\)O\(_2\): 298.0742.

2-[1-(t-Butylcarbonyl)indol-2-yl]indole-3-carbaldehyde (35a). A mixture of
1-(t-butoxycarbonyl)indole-2-boronic acid (34a) (1.17 g, 4.48 mmol), the 2-bromoindole-3-carbaldehyde (33) (500 mg, 2.24 mmol), 2M aqueous Na₂CO₃ (5.6 mL, 11.2 mmol) and PdCl₂(dpff) (2.0 mg, 2.0 mmol) in toluene (30 mL) was heated at 80 °C for 12 h. After being cooled to an ambient temperature, the reaction mixture was quenched with water and extracted with EtOAc. The EtOAc layer was washed with 2M NaOH and brine, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 15 g) using EtOAc-hexane (2:8, v/v) as an eluent to give the Boc-bisindole (35a) (800 mg, 99%), mp 170-172 °C (EtOAc). IR (ATR) ν: 1739, 1616 cm⁻¹; ¹H-NMR (CDCl₃) δ: 1.35 (9H, s), 6.92 (1H, s), 7.26-7.46 (5H, m), 7.63 (1H, d, J=7.7 Hz), 8.23 (1H, d, J=8.4 Hz), 8.40-8.43 (1H, m), 8.95 (1H, br s), 10.0 (1H, s); ¹³C-NMR (75 MHz) δ: 27.7, 84.9, 111.0, 115.7, 116.5, 117.4, 121.3, 122.2, 123.1, 123.6, 124.7, 125.0, 126.1, 126.7, 128.4, 135.5, 137.5, 140.8, 149.6, 186.3; MS m/z: 360 (M⁺); HR-MS (EI) m/z: 360.1458 (M⁺), calcd for C₂₂H₂₀N₂O₃: 360.1474.

2-[1-(Phenylsulfonyl)indol-2-yl]indole-3-carbaldehyde (35b). The same procedure as above was carried out using 1-(phenylsulfonyl)indole-2-boronic acid (34b) (150 mg, 0.50 mmol) to give the gummy bisindole (35b) (86 mg, 86%). ¹H-NMR (CDCl₃) δ: 6.91 (1H, s), 7.21-7.51 (10H, m), 8.41 (2H, m), 9.54 (1H, s); MS m/z: 400 (M⁺); HR-MS (EI) m/z: 400.0871 (M⁺), calcd for C₂₃H₁₆N₂O₃S: 400.0882.

2-(Indol-2-yl)indole-3-carbaldehyde (35c). A solution of the Boc-bisindole (35a) (400 mg, 1.11 mmol) in CF₃COOH (4 mL) was stirred under cooling with ice-water for 30 min. The reaction mixture was adjusted to pH 7 with 10% aqueous Na₂CO₃, and extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 30 g) using EtOAc-hexane (2:8, v/v) as an eluent to give the bisindole (35c) (278 mg, 96%), mp 274-276 °C (EtOAc-hexane). IR (ATR) ν: 1657 cm⁻¹; ¹H-NMR (DMSO-d₆) δ: 7.07-7.14 (1H, m), 7.19 (1H, s), 7.19-7.34 (3H, m), 7.50-7.57 (2H, m), 7.69 (1H, d, J=8.1 Hz), 8.20 (1H, d, J=8.1 Hz), 10.30 (1H, s), 12.08 (1H, br s), 12.51 (1H, br s); ¹³C-NMR (75 MHz, DMSO-d₆) δ: 104.4, 111.9, 112.0, 112.9, 120.2, 120.3, 120.8, 122.4, 123.2, 123.9, 126.7, 127.8, 127.9, 136.2, 137.2, 139.4, 185.4; MS m/z: 260 (M⁺); HR-MS (EI) m/z: 260.0925 (M⁺), calcd for C₁₇H₁₈N₂O: 260.0950.

N-Methoxymethyl-2-[N-(t-butyloxycarbonyl)indol-2-yl]indole-3-carbaldehyde (36a). A solution of the bisindole (35a) (70 mg, 0.19 mmol) in DMF (5 mL) was added to an ice-cooled suspension of 60% NaH (9.3 mg, 0.23 mmol) in DMF (2 mL). After being stirred at rt for 30 min, MOMCl (0.07 mL, 0.97 mmol) was added to the ice-cooled mixture. The reaction mixture was stirred at rt for 12 h and then poured into ice water. The mixture was extracted with EtOAc. The EtOAc layer was washed with water and brine, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 10 g) using EtOAc-hexane (3:7, v/v) as an eluent to give the gummy MOM-bisindole (36a) (58 mg, 73%). ¹H-NMR (CDCl₃) δ: 1.22 (9H, s), 3.20 (3H, s), 5.16 (1H, d, J=10.6
Hz) 5.48 (1H, d, J=10.6 Hz) 6.95 (1H, s), 7.34-7.41 (3H, m), 7.49 (1H, t, J=7.3 Hz), 7.56-7.59 (1H, m), 7.67 (1H, d, J=8.0 Hz), 8.32 (1H, d, J=8.4 Hz), 8.40-8.43 (1H, m), 9.86 (1H, s); MS m/z: 404 (M⁺); HR-MS (EI) m/z: 404.1739 (M⁺), calcd for C24H24N2O4: 404.1736.

N-Methoxymethyl-2-[N-(phenylsulfonyl)indol-2-yl]indole-3-carbaldehyde (36b). The same procedure as above was carried out using the bisindole 35b (52 mg, 0.14 mmol) to give the gummy bisindole 36b (63 mg, 98%). 1H-NMR (CDCl₃)  δ: 3.09 (3H, s), 5.42 (1H, d, J=11.4 Hz), 6.95 (1H, s), 7.26-7.68 (11H, m), 8.41-8.46 (2H, m), 9.12 (1H, s); MS m/z: 444 (M⁺); HR-MS (EI) m/z: 444.1157 (M⁺), calcd for C25H20N2O4S: 444.1144.

N-Methoxymethyl-2-(N-methoxymethylindol-2-yl)indole-3-carbaldehyde (36c). A solution of the bisindole 35c (278 mg, 1.1 mmol) in DMF (10 mL) was added to an ice-cooled suspension of 60% NaH (128 mg, 3.2 mmol) in DMF (5 mL). After being stirred at rt for 30 min, MOMCl (0.81 mL, 10.7 mmol) was added to another ice-cooled reaction mixture. The reaction mixture was stirred at rt for 12 h and then poured into ice water. The mixture was extracted with EtOAc. The EtOAc layer was washed with water and brine, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 10 g) using EtOAc-hexane (2:8, v/v) as an eluent to give the MOM-bisindole 36c (319 mg, 86%), mp 97-101 °C (EtOAc-hexane). IR (ATR) ν: 1655 cm⁻¹; 1H-NMR (CDCl₃)  δ: 3.16 (3H, s), 3.24 (3H, s), 5.18 (1H, d, J=7.7 Hz), 5.22 (1H, d, J=7.7 Hz), 5.38 (1H, d, J=11.0 Hz), 5.48 (1H, d, J=11.0 Hz), 6.92 (1H, s), 7.29 (1H, m), 7.42 (3H, m), 7.60 (2H, m), 7.74 (1H, d, J=7.7 Hz), 8.45 (1H, m), 9.81 (1H, s); 13C-NMR (75 MHz)  δ: 56.2, 56.4, 75.3, 75.5, 110.4, 110.5, 111.0, 119.3, 121.5, 122.5, 123.9, 124.1, 125.1, 126.1, 127.6, 137.2, 138.2, 140.7, 186.7; MS m/z: 348 (M⁺); HR-MS (EI) m/z: 348.1464 (M⁺), calcd for C21H20N2O3: 348.1474.

N-Methoxymethyl-2-(N-t-butylocarbonylindol-2-yl)-3-(1-hydroxyprop-2-yn-1-yl)indole (37a). A solution of ethynylmagnesium bromide (0.5M in THF, 1.2 mL, 0.60 mmol) was added to a stirred solution of the MOM-bisindole 36a (40 mg, 0.10 mmol) in THF (15 ml) under cooling with ice-water. After stirring at the same temperature for 1 h, the reaction mixture was quenched with an aqueous NH₄Cl (saturated) solution, which was extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 10 g) using EtOAc–hexane (2:8, v/v) as an eluent to give the MOM-bisindole 36a (40 mg, 0.10 mmol) in THF (15 ml) under cooling with ice-water. After stirring at the same temperature for 1 h, the reaction mixture was quenched with an aqueous NH₄Cl (saturated) solution, which was extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 10 g) using EtOAc–hexane (2:8, v/v) as an eluent to give the propargyl alcohol 37a as a mixture of diastereomers (30 mg, 70%). 1H-NMR (CDCl₃)  δ: 2.43 (0.5H, d, J=2.6 Hz), 2.57 (1H, d, J=2.6 Hz), 3.19 (4.5H, s), 3.20 (1.5H, s), 3.32 (3H, s), 5.51-5.18 (3H, m), 5.29-5.36 (3H, m), 5.40-5.43 (1H, m), 5.50-5.53 (0.5H, m), 6.83 (1H, s), 6.86 (1H, s), 7.23-7.35 (6H, m), 7.40-7.46 (2H, m), 7.54 (2H, d, J=8.1 Hz), 7.64 (2H, d, J=7.3 Hz), 8.05 (2H, m), 8.26 (1H, d, J=8.0 Hz), 8.34 (1H, d, J=8.0 Hz); MS m/z: 430 (M⁺); HR-MS (EI) m/z: 430.1901 (M⁺), calcd for C26H20N2O3: 430.1893.

N-Methoxymethyl-2-(N-phenylsulfonylcarbonylindol-2-yl)-3-(1-hydroxyprop-2-yn-1-yl)indole (37b).
The same procedure as above was carried out using the bisindole 36b as a mixture of diastereomers (32 mg, 0.073 mmol) to give the propargyl alcohol 37b (24 mg, 70%). $^1$H-NMR (CDCl$_3$) $\delta$: 2.57 (1H, d, $J$=1.9 Hz), 3.06 (3H, s), 4.89 (1H, d, $J$=11.0), 5.42 (1H, d, $J$=1.9 Hz), 6.86 (1H, s), 7.24-7.40 (5H, m), 7.45-7.63 (6H, m), 8.15 (1H, d, $J$=7.7 Hz), 8.36 (1H, d, $J$=8.4 Hz); MS m/z: 470 (M$^+$); HR-MS (EI) m/z: 470.1307 (M$^+$), calcd for C$_{27}$H$_{22}$N$_2$O$_4$S: 470.1300.

3-(1-Hydroxyprop-2-yn-1-yl)-N-methoxymethyl-2-(N-methoxymethylindol-2-yl)indole (37c).
The same procedure as above was carried out using the MOM-bisindole 36c (314 mg, 0.9 mmol) to give the propargyl alcohol 37c as a mixture of diastereomers (314 mg, 93%), mp 52-55 °C (EtOAc-hexane). IR (ATR) $\nu$: 3405 cm$^{-1}$; $^1$H-NMR (CDCl$_3$) $\delta$: 2.43 (0.5H, d, $J$=2.6 Hz), 2.57 (1H, d, $J$=2.6 Hz), 3.19 (4.5H, s), 3.20 (1.5H, s), 3.32 (3H, s), 5.51-5.18 (3H, m), 5.29-5.36 (3H, m), 5.40-5.43 (1H, m), 5.50-5.53 (0.5H, m), 6.80 (0.5H, s), 6.81 (1H, s), 7.22-7.37 (6H, m), 7.53-7.57 (3H, m), 7.69 (0.5H, d, $J$=7.7 Hz), 7.71(1H, d, $J$=7.7 Hz), 8.06 (0.5H, d, $J$=7.7 Hz), 8.20 (1H, d, $J$=7.7 Hz); $^{13}$C-NMR (75 MHz) $\delta$: 56.1, 56.2, 56.8, 57.3, 57.4, 73.5, 73.5, 74.5, 74.8, 75.0, 75.1, 83.1, 108.7, 109.4, 109.9, 110.4, 110.6, 118.0, 119.5, 120.4, 120.6, 121.1, 121.2, 121.2, 121.3, 121.3, 123.4, 123.6, 123.9, 125.3, 125.6, 127.8, 127.9, 128.1, 128.4, 137.4, 137.7, 138.1; MS m/z: 374 (M$^+$); HR-MS (EI) m/z: 374.1657 (M$^+$), calcd for C$_{23}$H$_{22}$N$_2$O$_3$: 374.1630.

N-Methoxymethyl-2-(N-methoxymethylindol-2-yl)-3-[(1-methoxymethyloxy)prop-2-yn-1-yl]indole (38). A solution of the propargyl alcohol 37c (314 mg, 0.84 mmol), MOMCl (0.38 mL, 5.04 mmol) and $i$-Pr$_2$NEt (1.16 mL, 6.72 mmol) in CH$_2$Cl$_2$ (10 mL) was heated at 50 °C for 12 h. After being cooled to ambient temperature, the reaction mixture quenched with water and extracted with CH$_2$Cl$_2$. The CH$_2$Cl$_2$ layer was washed with brine, dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 10 g) using EtOAc-hexane (1:9, v/v) as an eluent to give the MOM ether 38 (326 mg, 93%). $^1$H-NMR (CDCl$_3$) $\delta$: 2.51 (1H, d, $J$=2.2 Hz), 2.52 (0.5H, d, $J$=2.2 Hz), 3.11 (3H, s), 3.16 (3H, s), 3.17 (1.5H, s), 3.19 (3H, s), 3.30 (3H, s), 4.56 (0.5H, d, $J$=7.0 Hz), 4.64 (1H, d, $J$=7.0 Hz), 4.90 (0.5H, d, $J$=7.0 Hz), 4.93 (1H, d, $J$=7.0 Hz), 5.07 (1.5H, d, $J$=10.6 Hz), 5.14 (1H, d, $J$=10.6 Hz), 5.26 (1H, d, $J$=3.7 Hz), 5.33-5.43 (3.5H, m), 5.47 (0.5H, d, $J$=2.2 Hz), 6.79 (1.5H, s), 7.20-7.38 (6H, m), 7.53-7.58 (3H, m), 7.69 (1.5H, d, $J$=7.7 Hz), 8.06 (1.5H, t, $J$=7.7 Hz); $^{13}$C-NMR (75 MHz) $\delta$: 14.2, 21.0, 55.5, 55.6, 55.9, 56.0, 56.1, 60.4, 60.8, 74.4, 75.2, 75.2, 75.5, 81.1, 81.4, 93.3, 93.6, 108.4, 109.3, 110.4, 110.6, 110.7, 110.8, 115.5, 115.6, 120.8, 120.9, 120.9, 121.0, 121.2, 121.2, 123.3, 123.4, 123.7, 123.8, 125.8, 126.1, 127.9, 127.9, 128.0, 129.1, 129.3, 137.5, 137.6, 137.8, 137.9; MS m/z: 418 (M$^+$), HR-MS (EI) m/z: 418.1891 (M$^+$), calcd for C$_{25}$H$_{26}$N$_2$O$_3$: 418.1893.

6-Methoxymethyl-5-methyl-1,12-bis(methoxymethyl)indolo[2,3-a]carbazole (39). A solution of the MOM ether 38 (94 mg, 0.23 mmol) in THF (3 mL) was added to a solution of $t$-BuOK (126 mg, 1.12 mmol) in $t$-BuOH (7 mL). The stirred solution was heated at 90 °C for 1 h. After being cooled to rt, the solution was quenched with an aqueous NH$_4$Cl solution (saturated). The mixture was extracted with
EtOAc. The EtOAc layer was washed with brine, dried over Na$_2$SO$_4$, and concentrated. The residue was purified by column chromatography (silica gel, 10 g) using EtOAc-hexane (2:8, v/v) as an eluent to give the indolocarbazole 39 (87 mg, 93%), mp 138-140 °C (EtOAc-hexane). $^1$H-NMR (CDCl$_3$) δ: 2.96 (3H, s), 3.46 (3H, s), 3.47 (3H, s), 3.70 (3H, s), 5.28 (2H, s), 5.80 (2H, s), 5.82 (2H, s), 7.35 (2H, t, J=7.7 Hz), 7.47-7.52 (2H, m), 7.62 (2H, t, J=8.4 Hz), 8.24 (1H, d, J=8.4 Hz), 8.38 (1H, d, J=7.7 Hz); $^{13}$C-NMR (75 MHz) δ: 13.7, 55.8, 55.9, 58.2, 77.2, 78.0, 78.2, 100.0, 110.7, 110.9, 117.5, 118.4, 121.0, 121.4, 122.2, 122.5, 123.5, 123.9, 125.4, 125.6, 126.4, 127.3, 143.2, 144.0, 144.9; MS m/z: 418 (M$^+$); HR-MS (EI) m/z: 418.1896 (M$^+$), calcd for C$_{25}$H$_{26}$N$_2$O$_4$: 418.1893.

6-Methoxymethyloxy-1,12-bis(methoxymethyl)indolo[2,3-a]carbazole-5-carbaldehyde (40). DDQ (287 mg, 1.26 mmol) was added to a solution of the indolocarbazole 39 (240 mg, 0.57 mmol) in CH$_2$Cl$_2$ (30 mL). The reaction mixture was stirred at rt for 6 h, and filtrated through a Celite pad. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 20 g) using EtOAc-hexane (2:8, v/v) as an eluent to give the 5-formylindolocarbazole 40 (184 mg, 74%), mp 160-163 °C (EtOAc-hexane). IR (near) ν: 1666 cm$^{-1}$; $^1$H-NMR (CDCl$_3$) δ: 3.48 (3H, s), 3.48 (3H s), 3.67 (3H, s) 5.42 (2H, s) 5.71 (2H, s), 5.84 (2H, s), 7.35-7.46 (2H, m), 7.54-7.59 (2H, m), 7.62-7.66 (2H, m), 8.37 (1H, d, J=8.0 Hz), 9.15 (1H, d, J=8.0 Hz), 10.9 (1H, s); $^{13}$C-NMR (75 MHz) δ: 55.9, 56.1, 58.6, 77.2, 78.0, 78.6, 101.7, 110.9, 111.3, 116.6, 119.6, 121.5, 122.2, 122.6, 123.5, 124.9, 125.9, 126.2, 126.6, 127.2, 132.9, 143.1, 145.0, 154.2, 190.7; MS m/z: 432 (M$^+$); MS m/z: 432 (M$^+$); HR-MS (EI) m/z: 432.1698 (M$^+$), calcd for C$_{25}$H$_{24}$N$_2$O$_5$: 432.1685.

N-MOM-Calothrixin B (43). CAN (380 mg, 0.69 mmol) was added to a solution of the formylindolocarbazole 40 (35 mg, 0.08 mmol) in MeCN-H$_2$O (2:1, 5 mL) under cooling with ice-water. After being stirred at rt for 12 h, the reaction mixture was quenched with water and extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 5 g) using EtOAc-hexane (2:8, v/v) as an eluent to give the N-MOM-calothrixin B 43 (17 mg, 40%), mp 246-247 °C (EtOAc) (lit., $^{10}$ 234-235 °C). IR (ATR) ν: 2931, 2850, 1650 cm$^{-1}$; $^1$H-NMR (CDCl$_3$) δ: 3.45 (3H, s), 6.18 (2H, s), 7.48 (1H, t, J=8.1 Hz), 7.56 (1H, t, J=7.4 Hz), 7.68 (1H, d, J=8.1 Hz), 7.82 (1H, t, J=7.4 Hz), 7.91 (1H, t, J=6.6 Hz), 8.34 (1H, d, J=9.5 Hz), 8.47 (1H, d, J=8.4 Hz), 9.65 (1H, d, J=8.1 Hz), 9.81 (1H, s); $^{13}$C-NMR (75 MHz, DMSO-$d_6$) δ: 56.6, 75.4, 111.9, 118.5, 123.0, 123.1, 123.8, 124.2, 125.3, 127.6, 128.3, 130.2, 130.4, 131.5, 133.3, 135.4, 140.2, 147.8, 152.3, 181.3, 182.1; MS m/z: 342 (M$^+$); HR-MS (EI) m/z: 342.0997 (M$^+$), calcd for C$_{21}$H$_{14}$N$_2$O$_3$: 342.1004.

Calothrixin B (2). conc. HCl (3 mL) was added to a solution of the N-MOM-Calothrixin B 43 (50 mg, 0.15 mmol) in THF (15 mL) at rt. After being stirred at 50 °C for 48 h, the reaction mixture was quenched with a saturated NaHCO$_3$ solution and extracted with CHCl$_3$. The CHCl$_3$ layer was washed with brine,
dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 5 g) using EtOAc-hexane (2:8, v/v) as an eluent to give calothrixin B (2) (28 mg, 65%).

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REFERENCES AND NOTES


27. Data of 4-Hydroxy-2-phenylcarbazole-3-carbonitrile (20): mp 180-183°C (EtOAc-hexane); IR (ATR) v: 3386, 2202 cm⁻¹; ¹H-NMR (CDCl₃) δ: 7.09 (1H, s), 7.43-7.53 (6H, m), 7.63 (2H, d, J=7 Hz), 8.33 (1H, d, J= 8 Hz), 8.42 (1H, br s); MS m/z: 284 (M⁺).


