HETEROCYCLES, Vol. 82, No. 1, 2010, pp. 397 - 416. © The Japan Institute of Heterocyclic Chemistry
Received, 1st March, 2010, Accepted, 5th April, 2010, Published online, 7th April, 2010
DOI: 10.3987/COM-10-S(E)11

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 I.[8]

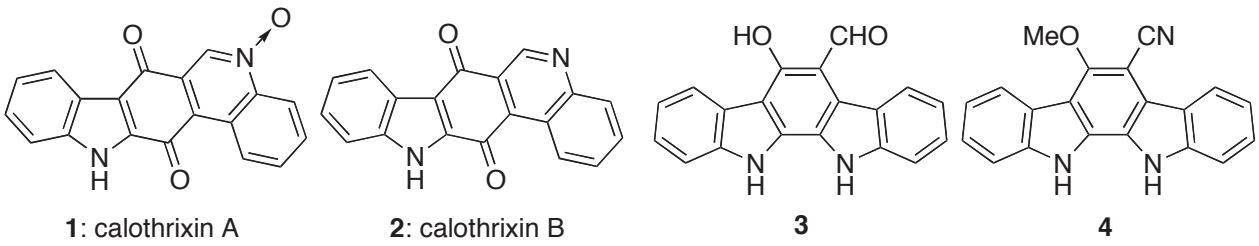
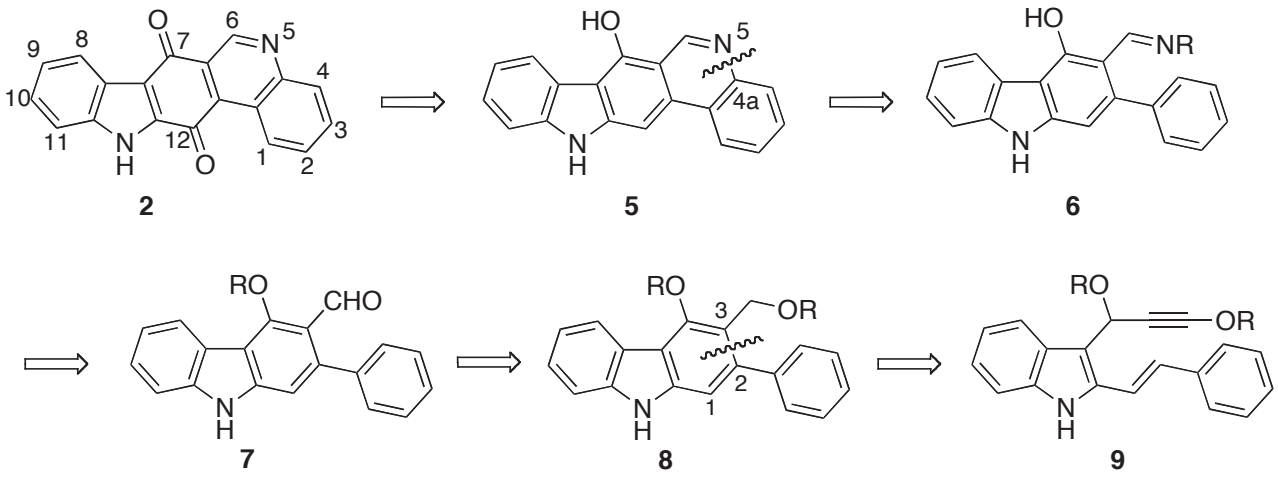


Figure 1

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 6π-electron system or an aza 6π-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 6π-electron system including the indole [*b*]-bond[15,22] or two indole [*b*]-bonds.[18,22]

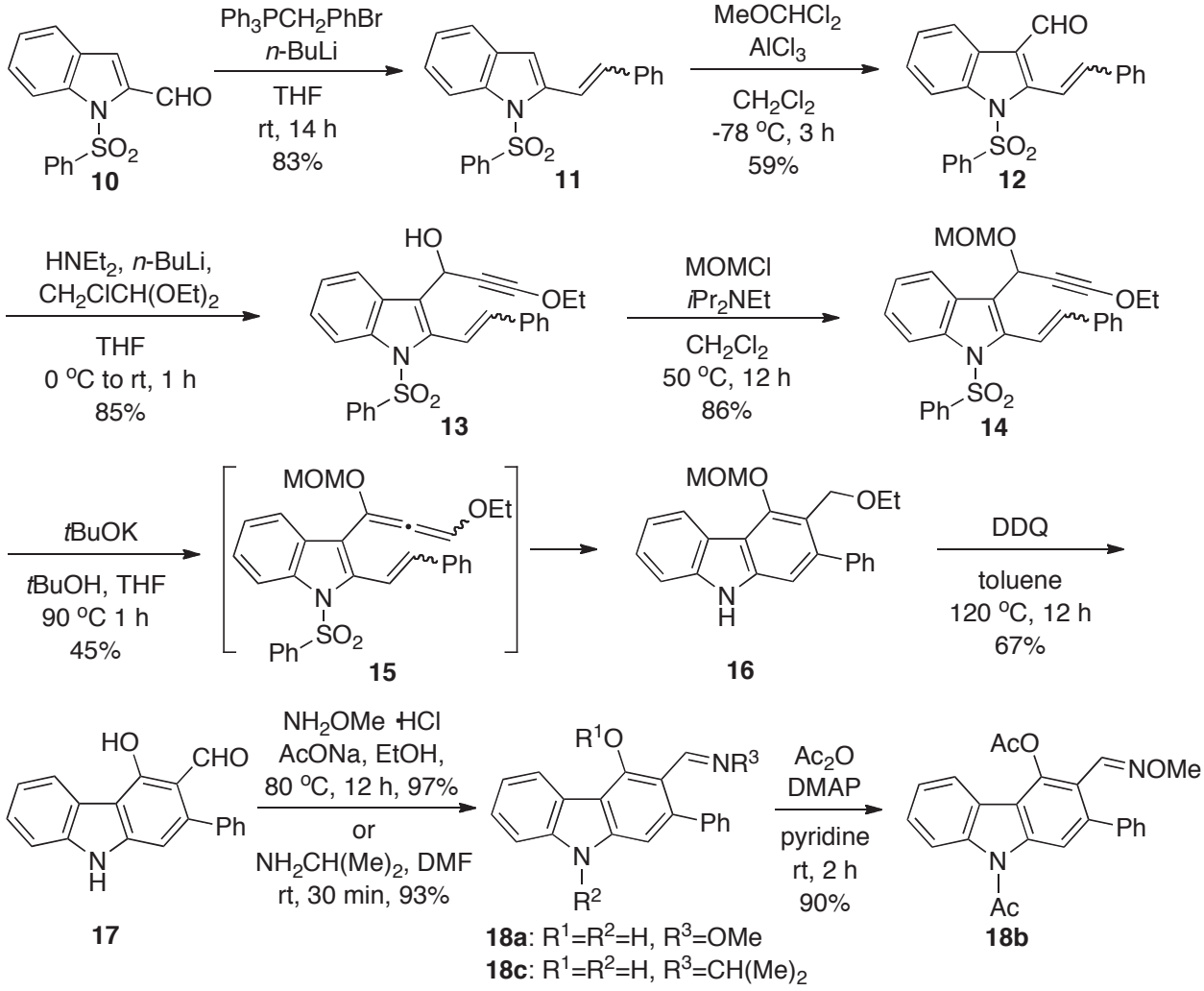
RESULTS AND DISCUTION



Scheme 1

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.[15,22]

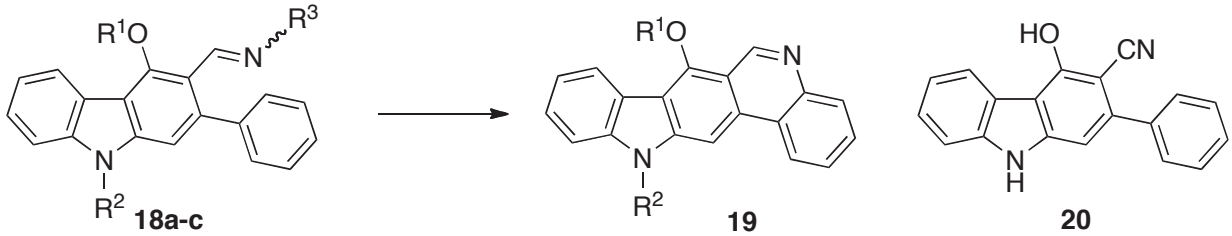


Scheme 2

To synthesize the 3-iminocarbazole **18**, we chose 2-formyl-*N*-phenylsulfonylindole **10**[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 $AlCl_3$[24] afforded the 2-alkenyl-3-formylindole **12** (59%). Treatment of **12** with lithium ethoxyacetylide prepared

from chloroacetaldehyde diethyl acetal according to Raucher's method[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 [22,26] to yield the desired 3-ethoxymethylcarbazole **16** along with elimination of the *N*-phenylsulfonyl group[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_2O and DMAP in pyridine yielded the *N*,*O*-diacetylcarbazole **18b** (90%).

Table 1. Synthetic Study of Indolo[3,2-*j*]phenanthridine by a Thermal or Microwave-assisted Electrocyclic Reaction

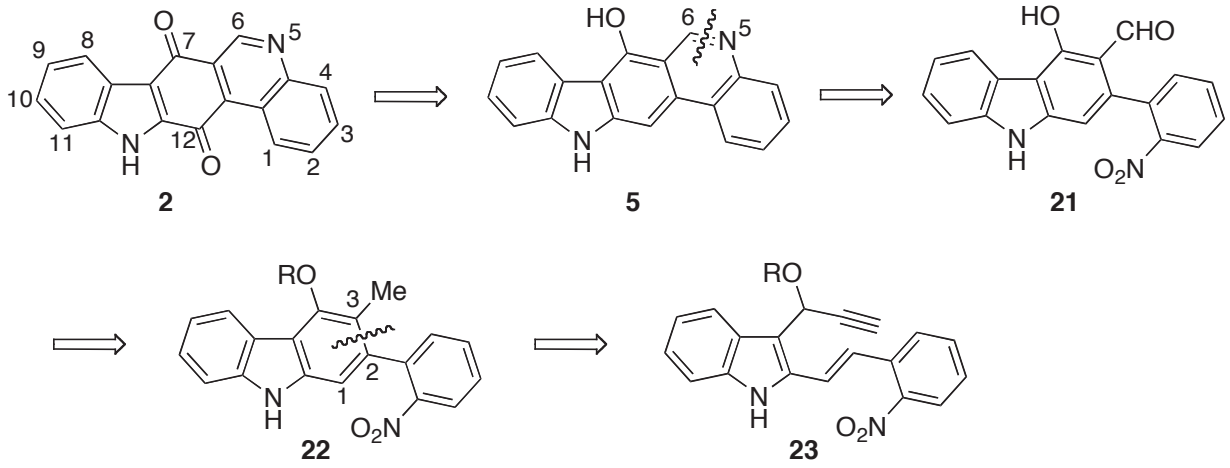


Entry	Starting Material	Solvent	Microwave*	Temp (°C)	Time (min)	Yield (%)	
						19	**20**
1	R^1=R^2=H, R^3=OMe	1,2-dichlorobenzene	-	180	4(h)	N.D.**	-
2	R^1=R^2=H, R^3=OMe	toluene/sealed tube	-	140	12(h)	N.D.	-
3	R^1=R^2=H, R^3=OMe	decalin	-	210	5(h)	N.D.	-
4	R^1=R^2=H, R^3=OMe	toluene	+	150	10	N.D.	-
5	R^1=R^2=H, R^3=OMe	DMF	+	210	5	N.D.	33
6	R^1=R^2=H, R^3=OMe	nitrobenzene	+	210	10	N.D.	-
7	R^1=R^2=Ac, R^3=OMe	1,2-dichlorobenzene	+	180	10	N.D.	-
8	R^1=R^2=Ac, R^3=OMe	DMF	+	210	60	N.D.	19
9	R^1=R^2=H, R^3=$CH(Me)_2$	DMF	+	210	45	N.D.	-

*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-*j*]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**[27] 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.

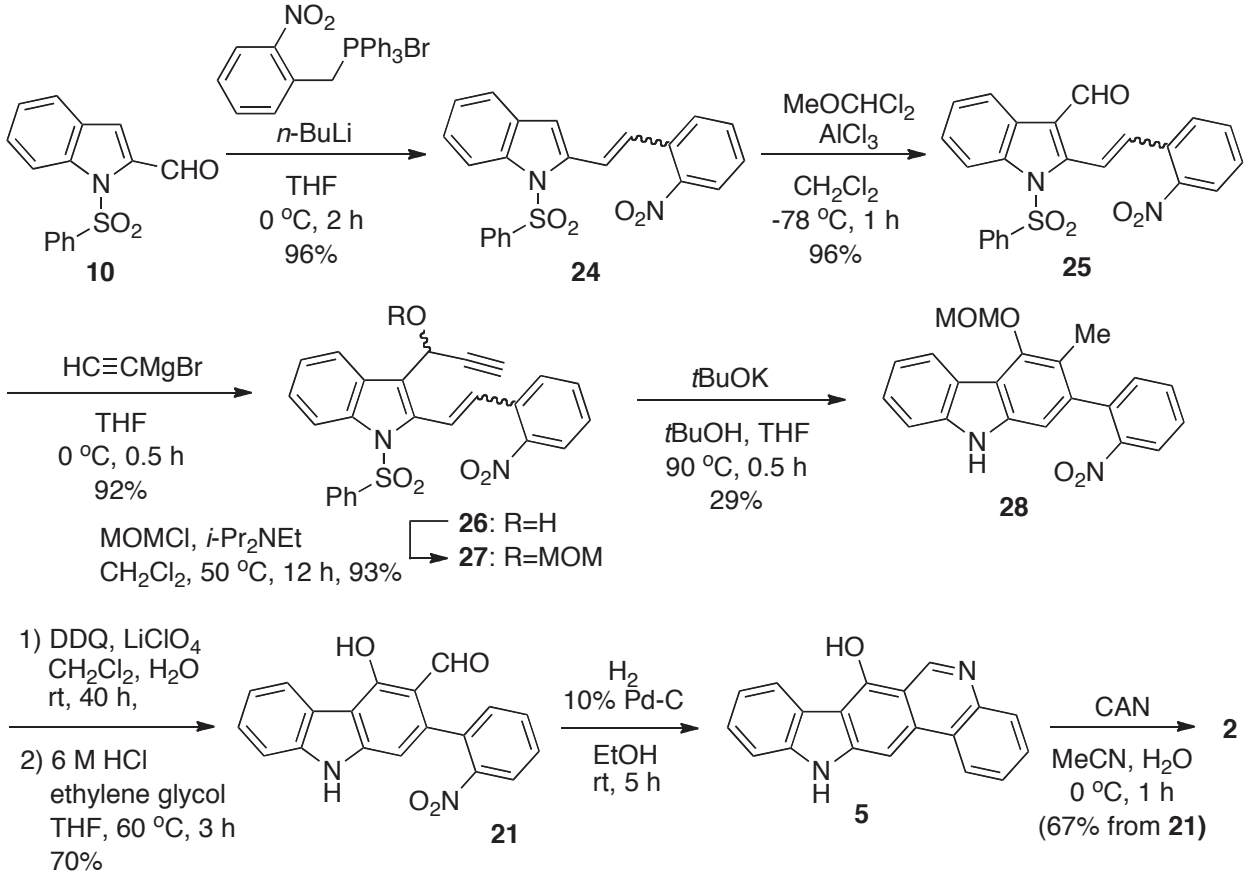


Scheme 3

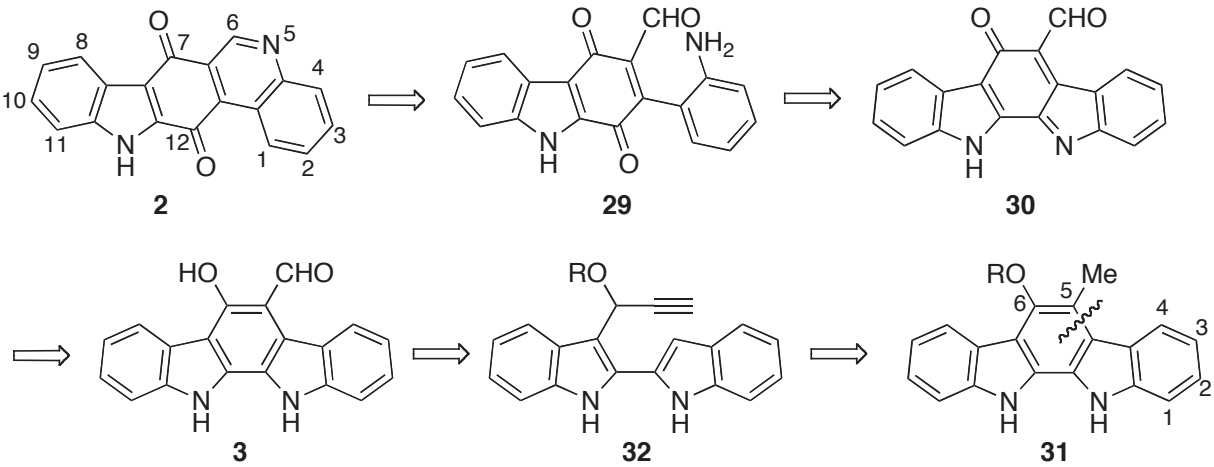
An alternative retrosynthetic route is depicted in Scheme 3. A 4-oxygenated 2,3,4-trisubstituted carbazole **21**, a derivative having a nitro group of **17**, was a key compound in Scheme 3. Therefore, the carbazole **21**, derived from a disconnection of the N5-C6 position of a pentacyclic phenol **5**, 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.[15,22]

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 $AlCl_3$ 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[22,26] to yield the desired 4-oxygenated 2,3,4-trisubstituted carbazole **28** along with elimination of the *N*-phenylsulfonyl group[22] in somewhat low yield (29%). Subsequent oxidation of **28** with DDQ in the presence of lithium perchlorate in CH_2Cl_2 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 H_2, 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**).[1] The total synthesis of calothrixin B (**2**) based on the retrosynthetic route (Scheme 3) was completed with a 10.7% overall yield.

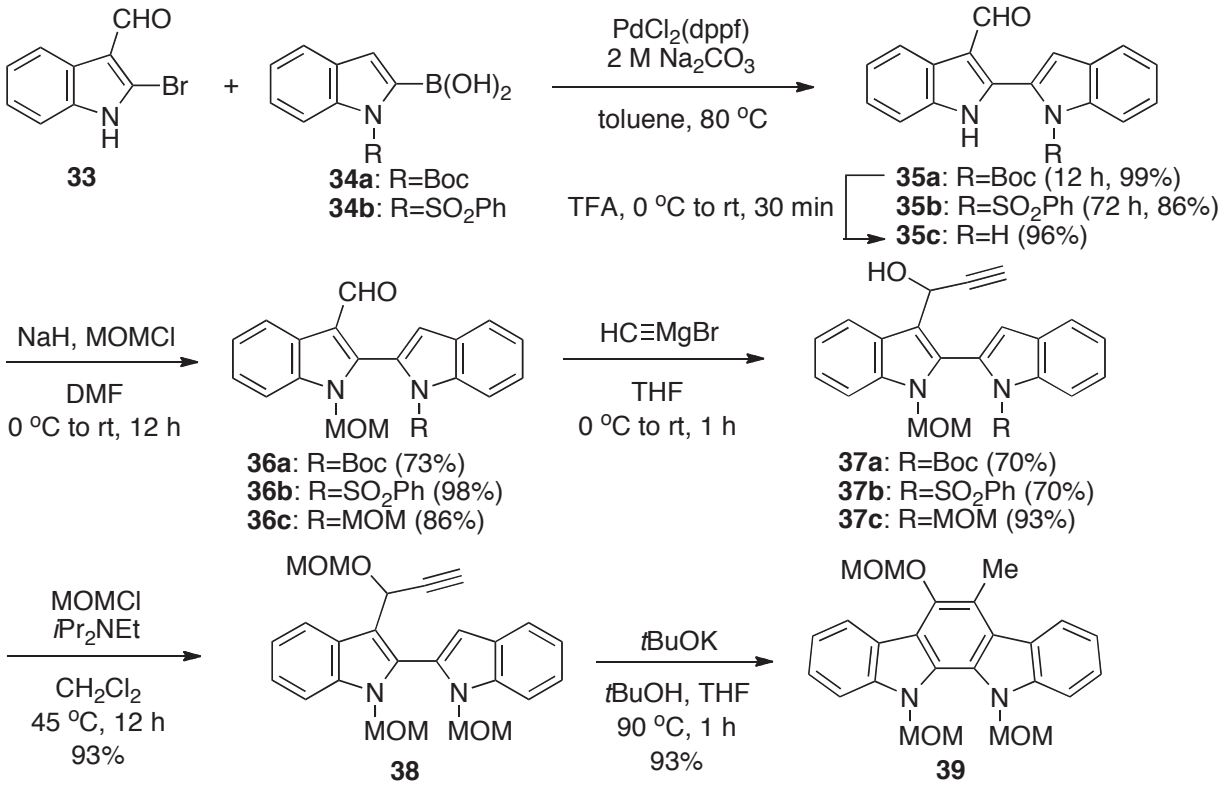


Scheme 4



Scheme 5

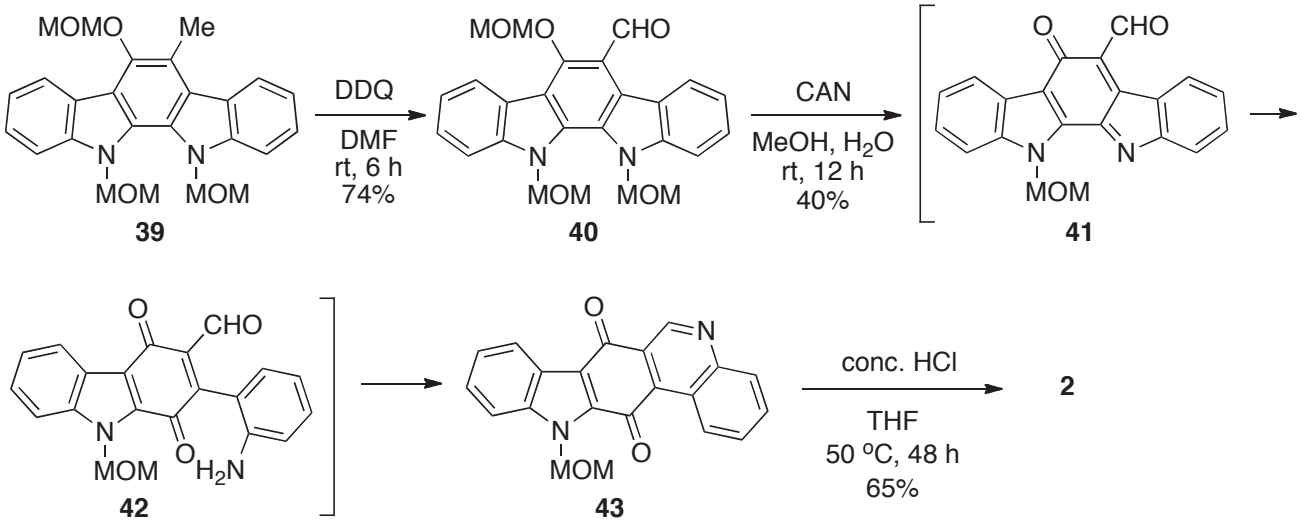
In a biomimetic route (Scheme 5), disconnection of the N5-C6 bond will produce a carbazole-1,4-quinone **29**, which is recyclized to an iminoquinone type of indolocarbazole **30**. An imino-quinone **30** is easily reduced to an indolo[2,3-*a*]carbazole **3**, which is a hypothetical metabolite, proposed by the Rickards group.[1] We envisioned that an important metabolite, 5-formyl-6-hydroxyindolo[2,3-*a*]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

We initially attempted the synthesis of the indolo[2,3-*a*]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**[28] as the starting material. A Suzuki-Miyaura cross-coupling reaction[29] of **33** with the indole-2-boronic acids **34a,b**[30] 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 [22,26] to yield the desired 6-oxygenated 5-methylindolo[2,3-*a*]carbazole **39** (93%).



Scheme 7

Sequential treatment of the fully protected **39** with DDQ in DMF gave the 5-formylindolo[2,3-*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-*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-*a*]carbazole **3** was synthesized from indigo by the Moody group.[19,20] Despite many attempts, however, they were unable to achieve oxidation of the non-protected indolo[2,3-*a*]carbazole **3** to obtain the pentacyclic calothrixin B (**2**). They then used our fully protected indolo[2,3-*a*]carbazole **40** to complete the total synthesis.[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-*j*]phenanthridine ring system **43**. Finally, cleavage of the *N*-MOM group using Kelly's method[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**)[15] and natural calothrixin B (**2**)[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-*j*]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).[10] 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.[1] Furthermore, a new synthetic pathway to a naturally occurring indolo[2,3-*a*]carbazole alkaloid is provided by this biomimetic route.[30]

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 $60PF_{254}$ (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 (^{1}H-NMR) spectra were recorded on a JEOL AL-300 at 300 MHz. Chemical shifts are reported relative to Me_4Si (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 (^{13}C-NMR) spectra were recorded on a JEOL AL-300 at 75 MHz. Chemical shifts are reported relative to $CDCl_3$ (δ 77.0) and DMSO-d_6 (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**[23] (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 NH_4Cl (saturated) solution and extracted with EtOAc. The

EtOAc layer was washed with brine, dried over Na_2SO_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) ν: 1369, 1173 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 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 $C_{22}H_{17}NO_2S$: 359.0980.

***N*-(Phenylsulfonyl)-2-styrylindole-3-carbaldehyde (12).** α,α-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_2Cl_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_2Cl_2. The CH_2Cl_2 layer was washed with brine, dried over Na_2SO_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) ν: 1658, 1385, 1176 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 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 $C_{23}H_{17}NO_3S$: 387.0929.

3-(3-Ethoxy-1-hydroxyprop-2-yn-1-yl)-*N*-(phenylsulfonyl)-2-styrylindole (13). To a solution of Et_2NH (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, chloroacetaldehyde 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_4Cl (saturated) solution, and then extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_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) ν: 3529, 2264, 1373, 1173 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, t, *J*=7 Hz), 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 $C_{27}H_{23}NO_4S$: 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_2NEt (1.51 mL, 8.67 mmol) in CH_2Cl_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_2Cl_2. The CH_2Cl_2 layer

was washed with brine, dried over Na_2SO_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 MOM ether **14** (469 mg, 86%). IR (ATR) ν: 2260, 1369, 1173 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 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 $C_{29}H_{27}NO_5S$: 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}; ^{1}H-NMR ($CDCl_3$) 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 $C_{19}H_{13}NO_2$: 287.0946.

4-Hydroxy-3-(methoxyiminomethyl)-2-phenylcarbazole (18a). A mixture of the 3-formylcarbazole **17** (30 mg, 0.105 mmol), $MeONH_2 \cdot HCl$ (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 Na_2SO_4, and concentrated under reduced pressure. The residue 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 oxime ether **18a** (32 mg, 97%), mp 175-177 °C (EtOAc-hexane). IR (ATR) ν: 3398 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 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 $C_{20}H_{16}N_2O_2$: 316.1212.

***N*-Acetyl-4-(acetyloxy)-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 Ac_2O (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 Na_2SO_4, 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}; ^{1}H-NMR ($CDCl_3$) 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 $C_{24}H_{20}N_2O_4$: 400.1423.

4-Hydroxy-3-(isopropyliminomethyl)-2-phenylcarbazole (18c). To a solution of the 3-formylcarbazole

17 (30 mg, 0.104 mmol) in DMF (5 mL) was added *i*-$PrNH_2$ (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_2SO_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) ν: 3375 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 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 $C_{22}H_{20}N_2O$: 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_4Cl (saturated) solution and extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_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) ν: 1516, 1365, 1338, 1170 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 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) δ: 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, 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 $C_{22}H_{16}N_2O_4S$: 404.0831.

2-[2-(2-Nitrophenyl)ethenyl]-*N*-(phenylsulfonyl)indole-3-carbaldehyde (25). α,α-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_2Cl_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_2Cl_2. The CH_2Cl_2 layer was washed with brine, dried over Na_2SO_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. IR (ATR) ν: 1670, 1520, 1369, 1342, 1173 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 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) δ: 114.3, 121.0, 121.5, 122.5, 125.1, 125.2, 125.6, 126.6, 126.8, 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 $C_{23}H_{16}N_2O_5S$: 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 NH_4Cl (saturated) solution, then extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4, 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}, ^{1}H-NMR ($CDCl_3$) 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); ^{13}C-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 $C_{25}H_{18}N_2O_5S$: 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*-Pr_2NEt (3.1 mL, 17.97 mmol) in CH_2Cl_2 (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 CH_2Cl_2. The CH_2Cl_2 layer was washed with brine, dried over Na_2SO_4, 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 (Et_2O-hexane). IR (ATR) ν: 1520, 1373, 1342, 1170 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 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); ^{13}C-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 $C_{27}H_{22}N_2O_6S$: 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 *t*-BuOK (223 mg, 1.99 mmol) in *t*-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 NH_4Cl solution (saturated). The mixture was extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4, 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}; ^{1}H-NMR ($CDCl_3$) 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) δ: 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 $C_{21}H_{18}N_2O_4$: 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_2Cl_2-H_2O (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_2Cl_2. The CH_2Cl_2 layer was washed with brine, dried over Na_2SO_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_2SO_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) ν: 3293, 1731, 1519, 1353 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 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) δ: 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 $C_{19}H_{12}N_2O_4$: 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_2O (2:1, 1 mL) was added to a solution of the resulting residue in MeCN-H_2O (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_2SO_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.,[1] >300 °C). IR (ATR) ν: 1731 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 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) δ: 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 $C_{19}H_{10}N_2O_2$: 298.0742.

2-[1-(*t*-Butylcarbonyl)indol-2-yl]indole-3-carbaldehyde (35a). A mixture of

1-(*t*-butoxycarbonyl)indole-2-boronic acid (**34a**)[30] (1.17 g, 4.48 mmol), the 2-bromoindole-3-carbaldehyde **33**[28] (500 mg, 2.24 mmol), 2M aqueous Na_2CO_3 (5.6 mL, 11.2 mmol) and $PdCl_2$(dppf) (2.0 mg, 2.0 mmol) in toluene (30 mL) was heated at 80 ºC 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 Na_2SO_4, 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}; ^{1}H-NMR ($CDCl_3$) 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); ^{13}C-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 $C_{22}H_{20}N_2O_3$: 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%). ^{1}H-NMR ($CDCl_3$) 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 $C_{23}H_{16}N_2O_3S$: 400.0882.

2-(Indol-2-yl)indole-3-carbaldehyde (35c). A solution of the Boc-bisindole **35a** (400 mg, 1.11 mmol) in CF_3COOH (4 mL) was stirred under cooling with ice-water for 30 min. The reaction mixture was adjusted to pH 7 with 10% aqueous Na_2CO_3, and extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4, 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}; ^{1}H-NMR (DMSO-d_6) 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); ^{13}C-NMR (75 MHz, DMSO-d_6) 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 $C_{17}H_{12}N_2O$: 260.0950.

***N*-Methoxymethyl-2-[*N*-(*t*-butylcarbonyl)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 Na_2SO_4, 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%). ^{1}H-NMR ($CDCl_3$) 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 $C_{24}H_{24}N_2O_4$: 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%). ^{1}H-NMR ($CDCl_3$) 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 $C_{25}H_{20}N_2O_4S$: 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 Na_2SO_4, 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}; ^{1}H-NMR ($CDCl_3$) 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); ^{13}C-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 $C_{21}H_{20}N_2O_3$: 348.1474.

***N*-Methoxymethyl-2-(*N*-*t*-butylcarbonylindol-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 NH_4Cl (saturated) solution, which was extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4, 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 **37** as a mixture of diastereomers (30 mg, 70%). ^{1}H-NMR ($CDCl_3$) 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 $C_{26}H_{26}N_2O_4$: 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 ($CDCl_3$) δ: 2.57 (1H, d, *J*=1.9 Hz), 3.06 (3H, s), 4.89 (1H, d, *J*=11.0), 5.32 (1H, d, *J*=11.0 Hz), 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 $C_{27}H_{22}N_2O_4S$: 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) ν: 3405 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 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), 6.80 (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, *J*=7.7 Hz); ^{13}C-NMR (75 MHz) δ: 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, 121.0, 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 $C_{23}H_{22}N_2O_3$: 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_2NEt (1.16 mL, 6.72 mmol) in CH_2Cl_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_2Cl_2. The CH_2Cl_2 layer was washed with brine, dried over Na_2SO_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 ($CDCl_3$) δ: 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) δ: 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 $C_{25}H_{26}N_2O_4$: 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_4Cl solution (saturated). The mixture was extracted with

EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_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 $C_{25}H_{26}N_2O_4$: 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_2Cl_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 $C_{25}H_{24}N_2O_5$: 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_2O (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_2SO_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 $C_{21}H_{14}N_2O_3$: 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_2SO_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%).

ACKNOWLEDGEMENTS

This work was partly supported by a Grant-in aid for Scientific Research (C) from the Japan Society for the Promotion of Science (JSPS).

REFERENCES AND NOTES

1. R. W. Rickards, J. M. Rothschild, A. C. Willis, N. M. de Chazal, J. Kirk, K. Kirk, K. J. Saliba, and G. D. Smith, *Tetrahedron*, 1999, **55**, 13513.
2. G. Knübel, L. K. Larsen, R. E. Moore, I. A. Levine, and G. M. L. Patterson, *J. Antibiot*., 1990, **43**, 1236.
3. H. Hayashi, S. Ohmoto, and M. Somei, *Heterocycles,* 1997, **45**, 1647; M. Somei, F. Yamada, Y. Suzuki, S. Ohmoto, and H. Hayashi, *Heterocycles,* 2004, **64**, 483; X. Cai and V. Snieckus, *Org. Lett.,* 2004, **6**, 2293.
4. N. T. Doan, R. W. Rickards, J. M. Rothschild, and G. D. Smith, *J. Appl. Phycol.,* 2000, **12**, 409.
5. N. T. Doan, P. R. Stewart, and G. D. Smith, *FEMS Microbiol Lett.,* 2001, **196**, 135.
6. X. X. Chen, G. D. Smith, and P. Waring, *J. Appl. Phycol.,* 2003, **15**, 269.
7. P. H. Bernardo, C. L. L. Chai, G. A. Heath, P. J. Mahon, G. D. Smith, P. Waring, and B. A. Wilkes, *J. Med. Chem*., 2004, **47**, 4958; P. H. Bernardo, C. L. L. Chai, M. Le Guen, G. D. Smith, and P. Waring, *Bioorg. Med. Chem. Lett*., 2007, **17**, 82.
8. Q. A. Kahn, J. Lu, and S. M. Hecht, *J. Nat. Prod*., 2009, **72**, 438.
9. T. Choshi and S.Hibino, *Heterocycles,* 2009, **77**, 85.
10. T. R. Kelly, Y. Zhao, M. Cavero, and M. Torneiro, *Org. Lett*., 2000, **2**, 3735.
11. P. H. Bernardo, C. L. L. Chai, and J. A. Elix, *Tetrahedron Lett.,* 2002, **43**, 2939.
12. P. H. Bernardo and C. L. L. Chai, *J. Org. Chem*., 2003, **68**, 8906.
13. D. Sissouma, S. C. Collet, and A. Y. Guingant, *Synlett,* 2004, 2612.
14. D. Sissouma, L. Maingot, S. Collet, and A. Guingant, *J. Org. Chem*., 2006, **71**, 8384.
15. S. Tohyama, T. Choshi, K. Matsumoto, A. Yamabuki, K. Ikegata, J. Nobuhiro, and S.Hibino, *Tetrahedron Lett*., 2005, **46**, 5263.
16. M.-L. Bennasar, T. Roca, and F. Ferrando, *Org. Lett*., 2006, **8**, 561.
17. P. H. Bernardo, W. Fitriyanto, and C. L. L. Chai, *Synlett,* 2007, 1935.
18. A. Yamabuki, H. Fujinawa, T. Choshi, S. Tohyama, K. Matsumoto, K. Ohmura, J. Nobuhiro, and S.

Hibino, *Tetrahedron Lett*., 2006, **47**, 5859.

19. J. Sperry, C. S. P. McErlean, A. M. Z. Slawin, and C. J. Moody, *Tetrahedron Lett*., 2007, **48**, 231.
20. C. S. P. McErlean, J. Sperry, A. J. Blake, and C. J. Moody, *Tetrahedron,* 2007, **63**, 10963.
21. S. Hibino and E. Sugino, In *Advances in Nitrogen Heterocycles* ed. by C. J. Moody, JAI Press, Greenwich, CT (USA), 1995, Vol. 5, pp 205; T. Kawasaki and M. Sakamoto, *J. Indian Chem. Soc*., 1994, **71**, 443; T. Choshi, *Yakugaku Zasshi,* 2001, **121**, 487; H.-J. Knölker and K. R. Reddy, *Chem. Rev*., 2002, **102**, 4303; H.-J. Knölker, *Top. Curr. Chem*., 2005, **244**, 115; K. Omura, T. Choshi, S. Watanabe, Y. Satoh, J. Nobuhiro, and S. Hibino, *Chem. Pharm. Bull*., 2008, **56**, 237; S. Kohno, S. Azuma, T. Choshi, J. Nobuhiro, and S. Hibino, *Tetrahedron Lett*., 2009, **50**, 590 and related references cited therein.
22. T. Choshi, T. Sada, H. Fujimoto, C. Nagayama, E. Sugino, and S. Hibino, *Tetrahedron Lett*., 1996, **37**, 2593; T. Choshi, H. Fujimoto, E. Sugino, and S. Hibino, *Heterocycles,* 1996, **43**, 1847; T. Choshi, T. Sada, H. Fujimoto, C. Nagayama, E. Sugino, and S. Hibino, *J. Org. Chem*., 1997, **62**, 2535; H. Hagiwara, T. Choshi, H. Fujimoto, E. Sugino, and S. Hibino, *Chem. Pharm. Bull*., 1998, **46**, 1948; H. Hagiwara, T. Choshi, H. Fujimoto, E. Sugino, and S. Hibino, *Tetrahedron,* 2000, **56**, 5807; H. Hagiwara, T. Choshi, J. Nobuhiro, H. Fujimoto, and S. Hibino, *Chem. Pharm. Bull*., 2001, **49**, 881; M. Hirayama, T. Choshi, T. Kumemura, S. Tohyama, J. Nobuhiro, and S. Hibino, *Heterocycles,* 2004, **63**, 1765; J. Nobuhiro, M. Hirayama, T. Choshi, S. Kamoshita, Y. Maruyama, Y. Sukenaga, T. Ishizu, H. Fujioka, and S. Hibino, *Heterocycles,* 2006, **70**, 491; S. Tohyama, T. Choshi, S. Azuma, H. Fujioka, and S. Hibino, *Heterocycles*, 2009, **79**, 955.
23. M. G. Saulnier and G. W. Gribble, *J. Org. Chem*., 1982, **47**, 757.
24. M. Tani, T. Aoki, S. Ito, S. Matsumoto, M. Hideshima, K. Fukushima, R. Nozawa, T. Maeda, M. Tashiro, Y. Yokoyama, and Y. Murakami, *Chem. Pharm. Bull*., 1990, **38**, 3261.
25. S. Raucher and B. L. Bray, *J. Org. Chem*., 1987, **52**, 2332.
26. K. Hayakawa, S. Ohsuki, and K. Kanematsu, *Tetrahedron Lett*., 1986, **27**, 4205; S. Nagashima and K. Kanematsu, *Tetrahedron: Asymmetry,* 1990, **1**, 743.
27. Data of 4-Hydroxy-2-phenylcarbazole-3-carbonitrile (**20**): mp 180-183ºC (EtOAc-hexane); IR (ATR) ν: 3386, 2202 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 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^+).
28. M. Somei, S. Sayama, K. Naka, and F. Yamada, *Heterocycles,* 1988, **27**, 1585.
29. K. Takahashi, J. Takagi, T. Ishiyama, and N. Miyaura, *Chem. Lett*., 2000, 126.
30. E. Vazquez, I. W. Davies, and J. F. Payack, *J. Org. Chem*., 2002, **67**, 7551.
31. H. Nakano and S. Omura, *J. Antibiot*., 2009, **62**, 17.