Pergamon

Tetrahedron 56 (2000) 7163–7171

TETRAHEDRON

Synthesis of Optically Pure Clausenamine-A and its Demethoxylated Analogs

Guoqiang Lin* and Aimin Zhang

Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, People's Republic of China

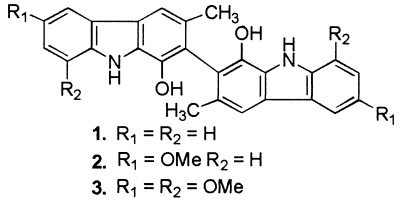
Received 12 June 2000; accepted 18 July 2000

Abstract—The first total synthesis of Clausenamine-A (**3**) was developed involving the Suzuki cross-coupling and oxidative coupling reaction. The synthesis of its demethoxylated analogs **1** and **2** were also reported. Resolution of (+)-**1**, (+)-**2**, (+)-**3** and (−)-**1**, (−)-**2**, (−)-**3** were performed via their corresponding camphorsulfonates of the racemates. The absolute configurations of (+)-**1**, (+)-**2**, (+)-**3** and (−)-**1**, (−)-**2**, (−)-**3** were assigned as (a*R*) and (a*S*), respectively, by X-ray analysis and their CD spectrum. The primarily cytotoxic activities of these biscarbazoles against *Plasmodium falciparum* were briefly described.

Introduction

A number of dimeric carbazole alkaloids have been isolated from different natural sources during the past years, which exhibited various biological activities including anti-tumor, anti-inflammatory and cytotoxic activities.[1,4] In 1996, Clausenamine-A (**3**) was isolated from the stem and root bark of *Clausena excavata*,[2] which is used as the Chinese folk medicine for detoxication treatment caused by the poisonous snakebite. Recently, dimeric *O*-demethyl-murrayafoline A (**1**) was found to exhibit antiplasmodial activity against *Plasmodium falciparum* in vitro.[3] In the previous communications, the synthesis of these biscarbazoles and the evaluation of their biological activities against cancer cells were reported.[4,5]

Due to the restricted rotation around the central biaryl axis, **1**, **2** and **3** are structurally atropisotopic. However, little attention has been paid to the relationship between the stereochemistry and the biological activity.[6] Herein, we report the first synthesis of the optically pure Clausenamine-A (**3**) and its demethoxylated analogs **1** and **2**, in which the regioselective oxidative coupling of synthetic phenolic monomer (**21**) and the enantioresolution of (±)-**3** were employed as the key steps. The absolute configurations of (+)-**1**, (+)-**2**, (+)-**3** and (−)-**1**, (−)-**2**, (−)-**3** were assigned as (a*R*) and (a*S*), respectively, by X-ray analysis and their CD spectra.



1. $R_1 = R_2 = H$
2. $R_1 = OMe$ $R_2 = H$
3. $R_1 = R_2 = OMe$

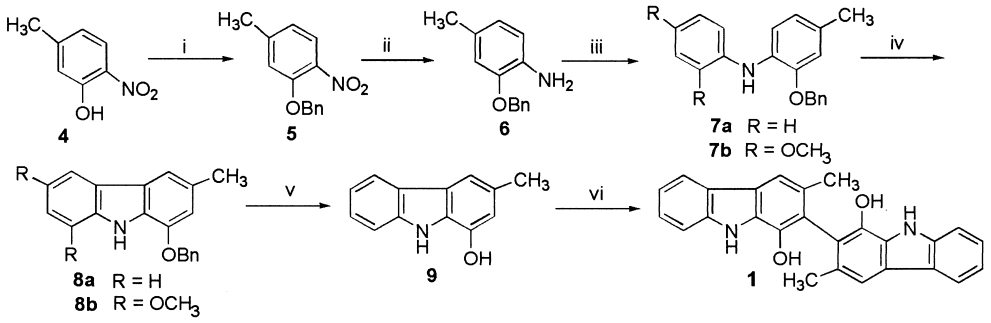
Synthesis

As shown in Scheme 1, the hydroxyl group of **4** was protected as the benzyl ether, and the resulting product **5** was reduced by ferrum to yield **6**. When compound **6** was subjected to the Goldberg coupling reaction[7a,b] or the Ullmann coupling reaction,[7c] the desired product **7a** was obtained in poor yields. After several attempts, amination of **6** was achieved with satisfaction under Buchwald condition[7d,e] to afford **7a** in 93% yield. Cyclization of the *N*-phenyl-2-benzyloxy-4-methylaniline (**7a**) with $Pd(OAc)_2$ in acetic acid gave **8a** in 32% yield.[8] The low yield of the cyclization is possible caused by the electron-donating effects of the methyl and the benzyloxyl substitution in the benzene ring. Catalytic hydrogenation of **8a** afforded the *O*-demethyl-murrayafoline A (**9**) in 73% yield. Oxidative coupling of the phenolic monomer (**9**) was completed by aerial treatment of **9** with $(t\text{-BuO})_2$ in chlorobenzene, providing the racemic dimeric *O*-demethyl-murrayafoline A (**1**) in 87% yield.[9] Lower yield was obtained when this oxidative coupling was performed under argon atmosphere. In the presence of oxygen, the radicals were preferentially provided which cause the termination of the desired reaction. The desired coupling site was confirmed by the disappearance of the signal of 2-H in the ^{1}H NMR spectrum and the analysis on X-ray spectrum.

Keywords: *Plasmodium falciparum*; clausemine-A; Suzuki cross-coupling reaction; resolution.

* Corresponding author. Tel.: +86-21-641-63300; fax: +86-21-641-66263; e-mail: lingq@pub.sioc.ac.cn

0040–4020/00/$ - see front matter
PII: S0040-4020(00)00634-7

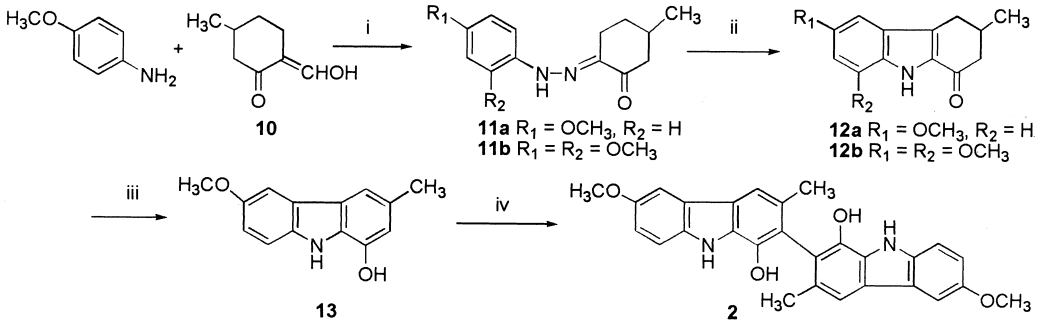


Scheme 1. *Reagents and conditions:* (i) $PhCH_2Br$, NaOH, DMSO, 86%; (ii) Fe, H_2O, NH_4Cl, reflux, 83%; (iii) Pd_2(dibenzylideneacetone)$_3$, 2,2′-bis(diphenylphosphine)-1,1′-binaphthyl, 18-C-6, *t*-BuONa, THF, 40°C, iodobenzene for **7a**, 93%, 2,4-dimethoxyl-indobenzene for **7b**, 77%; (iv) $Pd(OAc)_2$, HOAc, reflux, 32%; (v) 10% Pd/C, H_2, 73%; (vi) (*t*-BuO)$_2$, chlorobenzene, reflux, 87%.

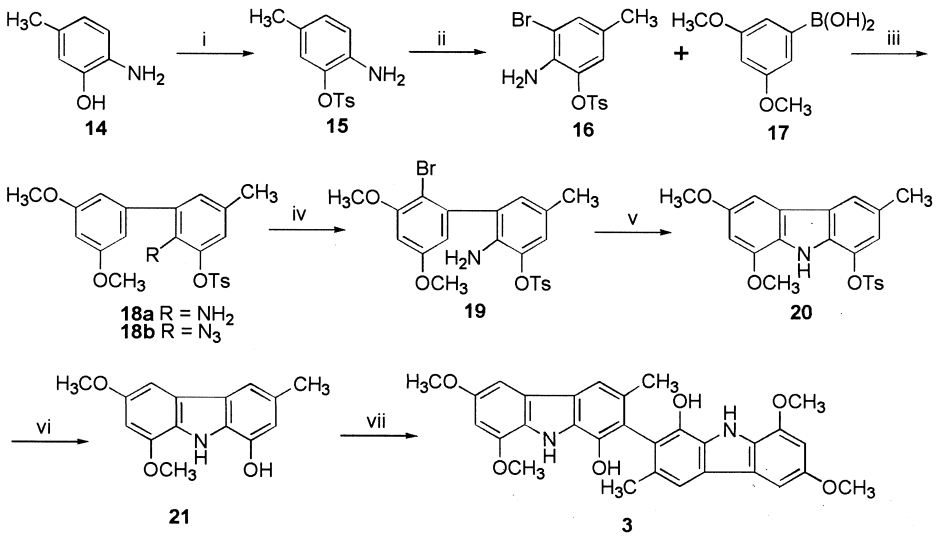
After accomplishing the synthesis of racemic dimeric *O*-demethyl-murrayafoline A (**1**), the similar manner was employed to synthesize Clausenamine-A (**3**). However, the cyclization of **7b** using palladium acetate failed to afford the desired product **8b**, probably due to the electrondonating effects exerted by the methoxyl groups in the benzene ring, which decrease the Pd oxidative addition activity. Thus, another approach to **2**, the analog of **1**, was taken as a model study (Scheme 2). The Japp–Klingmann condensation[10]of *p*-methoxybenzenediazonium chloride with **10** resulted in hydrazone **11a**, which cyclized to give **12a**.[11] Treatment of **12a** with 10% Pd/C in a sealed tube furnished **13** in 73% yield. The next oxidative coupling of **13** provided **2** in 82% yield. The cyclization of **11b** was employed to gain the product **12b**. Surprisingly, by using several reaction conditions such as TsOH/benzene,[12a] $BF_3'\cdot Et_2O$/AcOH,[12b] $BF_3\cdot Et_2O$/EtOAc,[12b] the cyclization of **11b** was unsuccessful. It is, as mentioned above, probably due to the electron-donating effects of the methoxyl groups in the benzene ring.

As mentioned above, owing to the electro-donating effects of the two methoxyl groups in the benzene ring, the desired product can not be obtained through $Pd(OAc)_2$ catalyzed cyclization of *N*-(2,4-dimethoxy)-phenyl-2-benzyloxy-4-methylaniline (**7b**) and cyclization of 4-methyl-cyclohexane-1,2-dione-1-(3,5-dimethoxy)-phenylhydrone (**11b**).[5] Therefore, another synthetic route starting from the commercially available 2-amino-5-methylphenol **14** was employed, as depicted in Scheme 3. Firstly, in order to introduce a bromine atom *ortho*-positioned to the amine group, it is needed to protect the free hydroxyl group in **14**. Having tried the use of several protected groups, tosylate **15**[13] was employed as the electron-withdrawing group. Compound **16** was gained through electrophilic aromatic bromination[14] of **15** using bromo-dimethylsulfonium bromide generated in situ. The brominate position substituted in the *ortho* position of the amino group was confirmed by NOE effects (94% yield). The required biphenyl **18** was prepared quantitatively by Suzuki cross-coupling of 3,5-dimethoxyphenyl boronic acid (**17**)[15] and **16** with 5% $Pd(PPh_3)_4$ and 2N aqueous Na_2CO_3 in benzene.[16] Conversion of the amine **18a** to toluene-4-sulfonic acid 2-azido-3′,5′-dimethoxy-5-methyl-biphenyl-3-yl ester **18b** by diazotization followed by treatment with sodium azide[17] has been tried. Unfortunately it failed to complete this procedure; the same was met while the detosylate of **18a** was used. Analysis of the electron distributing of **18a** through the semiempirical MO calculation using the Hyperchem programs disclosed that the phenyl ring bearing two methoxyl groups is electron abundant, which fits for the electrophilic bromination procedure. Bromination of **18a** using 48% HBr in DMSO afforded compound **19** in 79.5% yield.[14] The five-member ring closure was successfully performed through a palladium(0) mediated cyclization[18] of compound **19** which provided 9-H-carbazole **20** in 97% yield. Detosylation of **20** gave the monomer **21**. Oxidative coupling of the phenolic monomer **21** was completed by aerial treatment of **21** with (*t*-BuO)$_2$ in chlorobenzene offering the racemic clausenamine-A (**3**) in 90% yield.[8] The structure of **3** was characterized fully by spectroscopic analysis.

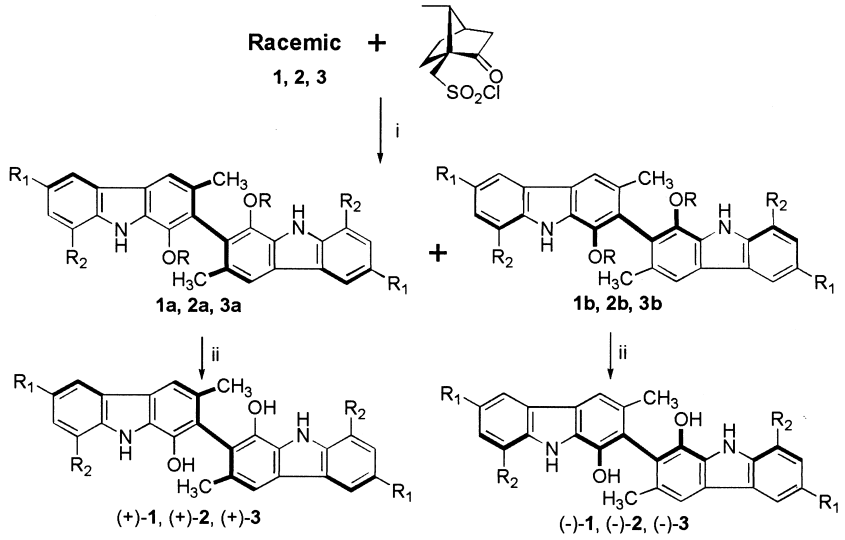
After accomplishing the synthesis of racemic Clausenamine-



Scheme 2. *Reagents and conditions:* (i) HCl, $NaNO_2$, CH_3COONa, 54%; (ii) HOAc, HCl, reflux, 44%; (iii) 10% Pd/C, 220–240°C, 73%; (iv) (*t*-BuO)$_2$, chlorobenzene, reflux, 82%.



Scheme 3. *Reagents and conditions:* (i) TsCl, Et_3N, CH_2Cl_2, rt, 84%; (ii) 48% HBr, DMSO, rt, 94%; (iii) 5% $Pd(PPh_3)_4$, 2N Na_2CO_3, benzene, 3,5-dimethoxyphenyl boronic acid, ethanol, reflux, 99%; (iv) 48% HBr, DMSO, rt, 79.5%; (v) 1.2 equiv. $Pd(PPh_3)_4$, Na_2CO_3, toluene, reflux, 97%; (vi) KOH, H_2O, EtOH, reflux, 88%; (vii) (*t*-BuO)$_2$, chlorobenzene, reflux, 90%.



Scheme 4. *Reagents and conditions:* (i) Et_3N, (*S*)-camphorsulfonylchloride, CH_2Cl_2, reflux, 94%, then chromatographic separation of **3a** and **3b** (silica gel, eluent; $CH_2Cl_2/CHCl_3$/ether=50:1:2); (ii) KOH, EtOH, rt, (+)-**3**, 84%, (−)-**3**, 87%.

A (**3**) and its demethoxylated analogs **1** and **2**, it is turned to get the optically pure ones through resolution of these racemic biscarbazoles. Resolution of these racemates was accomplished by silica gel column chromatography of their corresponding (+)-camphorsulfonates[19] using $CH_2Cl_2/CHCl_3/Et_2O$ (50:1:2) as the eluant (Scheme 4). Some physical properties of these corresponding (+)-camphorsulfonates were listed in Table 1. Recrystallization of **1a** from ethanol provided a colorless prism, which is good for X-ray diffraction.[5] The absolute stereochemistry of the diester **1a** was determined as (a*R*) by correlation with the known absolute configuration of (*S*)-camphorsulfonate moiety within the molecular.

Treatment of **1a**, **1b**, **2a**, **2b**, **3a** and **3b** with KOH in EtOH and water afforded their corresponding optically pure

Table 1. Some physical properties of **1a**, **1b**, **2a**, **2b**, **3a** and **3b**

Entry	Resolution yield (%)	Mp (°C)	$[\alpha]_D^{21}$	AB signals ($-CH_2SO_2-$) in ^{1}H NMR (300 Hz)
1a	48	177–179	+3.75° (*c* 0.1, $CHCl_3$)	3.48 (2H, d, *J*=14.8 Hz), 2.23 (2H, d, *J*=14.8 Hz) ppm
1b	46	132–134	+15.2° (*c* 0.48, $CHCl_3$)	3.13 (2H, d, *J*=14.9 Hz), 2.53 (2H, d, *J*=14.8 Hz) ppm
2a	41	235–237	+38.1° (*c* 1.08, $CHCl_3$)	3.47 (2H, d, *J*=14.9 Hz), 2.25 (2H, d, *J*=14.9 Hz) ppm
2b	47	203–204	−34.9° (*c* 1.14, $CHCl_3$)	3.13 (2H, d, *J*=14.8 Hz), 2.53 (2H, d, *J*=14.9 Hz) ppm
3a	47	167–168	+7.7° (*c* 0.65, $CHCl_3$)	3.43 (2H, d, *J*=14.8 Hz), 2.17 (2H, d, *J*=14.8 Hz) ppm
3b	47	148–150	−5.9° (*c* 0.55, $CHCl_3$)	3.08 (2H, d, *J*=14.8 Hz), 2.48 (2H, d, *J*=14.9 Hz) ppm

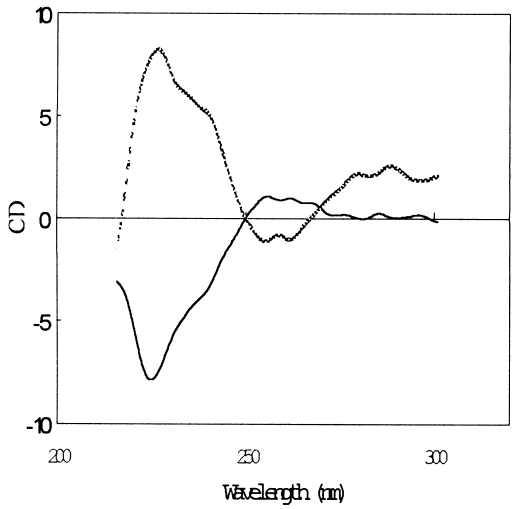


Figure 1. The CD spectrum of (+)-**3** and (−)-**3** (solid line stands for (+)-**3** and dashed lines represents (−)-**3**.

As shown in Table 3, Clauseamine-A (**3**) and its demethoxylated analogs **1** and **2** exhibited moderate cytotoxic activities. From the table it was also concluded that as the number of methoxyl group increases, the activities are decreasing. To our disappointment, the chiral biscarbazoles did not show any increase activities compared with the racemic one.

In summary, we have accomplished the first synthesis of the optically pure (*R*)- and (*S*)-Clauseamine-A (**3**) and its demethoxylated analogs **1** and **2**. The absolute configurations of (+)-**1**, (+)-**2**, (+)-**3** were established as a*R*, and the ones of (−)-**1**, (−), (−)-**3** should be a*S* based on X-ray analysis and CD spectrum. We also found these biscarbazoles exhibited moderate antimalarial activities.

Experimental

Distillation of the products was performed using Kugelrohr (Buchi); the boiling points are indicated by air-bath temperature values without any correction. The NMR spectra (^{1}H) was recorded on a Varian GEMINI 300 spectrometer in $CDCl_3$; tetramethylsilane (TMS) was used as the internal standard. The IR spectra was determined on a JASCO IR-810 spectrometer. Unless mentioned elsewhere, the reactions were performed in argon atmosphere.

Table 2. Some physical data of (+)-**1**, (+)-**2**, (+)-**3** and (−)-**1**, (−)-**2**, (−)-**3**

Entry	$[\alpha]_D^{21}$ (Solvent: $CHCl_3$)	Yield (%)	(+)-Cotton effect (nm)	(+)-Cotton effect (nm)
(+)-**1**	+29.9° (*c* 0.67)	73.2	256.6	227.4
(−)-**1**	−39° (*c* 0.1)	94	227.6	257.4
(+)-**2**	+44.3° (*c* 0.09)	57	256.4	228.6
(−)-**2**	−44.7° (*c* 0.13)	90	229	258.4
(+)-**3**	+142.2° (*c* 0.75)	84	256	225
(−)-**3**	−147.6° (*c* 0.65)	87	227	225

Table 3. The cytotoxic activities against *Plasmodium falciparum* in vitro

Sample	D6[a] IC_{50} (μg/ml)	W2[a] IC_{50} (μg/ml)
(±)-**1**	1.357	1.215
(±)-**2**	3.196	3.395
(±)-**3**	3.219	3.375
(+)-**3**	4.387	4.256
(−)-**3**	3.382	3.337

[a] D6 is the chloroquine-sensitive clone, and W2 is the chloroquine-resistant clone.

biscarbazoles, respectively. The CD spectrum of (+)-**3** and (−)-**3** were illustrated in Fig. 1. The structure of (+)-**3** was confirmed by the CD spectrum which showed the first (positive) cotton effect at 256 nm and the second (negative) one at 225 nm, while its isomer (−)-**3** showed the first (negative) cotton effect at 255 nm and the second (positive) one at 227 nm. Some physical data of these optically pure biscarbazoles were listed in Table 2. From the X-ray analysis and CD spectrum, the absolute configurations of (+)-**1**, (+)-**2**, (+)-**3** were established as a*R*, and those of (−)-**1**, (−)-**2**, (−)-**3** should be a*S*.[20]

Cytotoxicity Activities

In the previous report, the racemic biscarbazoles (**1**, **2** and **3**) showed moderate activities against cancer cells.[4] Here their cytotoxic activities against *P. falciparum* were reported.

1-Nitro-2-benzyloxy-4-methyl-benzene (5). To a suspension of 2-nitro-cresol (3.06 g, 20 mmol) in DMSO (30 ml), NaOH (1.6 g, 40 mmol) was added with stirring. 15 min later, benzyl bromide (6 ml, 50 mmol) was added. The stirring was kept until the disappearance of the starting material monitored by TLC, the products were quenched with water (20 ml) and the aqueous layer was extracted with CH_2Cl_2 (2×30 ml). The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent was removed in vacuo. The residue was purified by recrystallization from ether to give **5** as a yellow solid (4.20 g, 86%). Mp 54–55°C. FT-IR(KBr): 1613, 1591, 1507, 1454, 1336, 1267, 1178, 1035, 1013, 817, 731 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82 (d, 1H, *J*=8.3 Hz, 6-*H*), 7.26–7.49 (m, 5H, Bn-*H*), 6.93 (s, 1H, 3-*H*), 6.83 (d, 1H, *J*=8.1 Hz, 5-*H*), 5.22 (s, 2H, $-OCH_2$), 2.39 (s, 3H, $-CH_3$) ppm. MS *m*/*z* (EI, 70 eV): 288, 271, 228, 181, 137, 91 (100), 77, 65, 51. EA: Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.10; H, 5.28; N, 5.83.

2-Benzyloxy-4-methyl-aniline (6). A flask charged with ferrum (280 mg, 5 mmol), NH_4Cl (35 mg, 0.65 mmol), water (8 ml), was warmed to reflux for 15 min, followed by addition of **5** (243 mg, 1 mmol). The mixture was

refluxed for 1.5 h under vigorous stirring. After the completion of the reaction, the solution was cooled to room temperature, 5% $NaHCO_3$ was added to adjust the pH to between 7 and 8. Then filtrated and the filtrate was extracted with ethyl acetate (2×30 ml). The combined organic layers were washed with brine and then washed with 5% aqueous HCl. The water layer was neutralized by addition of 20% NaOH, extracted with ethyl acetate (3×30 ml), finally dried over Na_2SO_4. Removal of the solvent provided the product **6** (177 mg, 83%). Mp 75–76°C. FT-IR(KBr): 3464, 3374, 3033, 920, 1620, 1596, 1239, 1156, 1018, 809, 759, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.31–7.46 (m, Bn-*H*), 6.70 (s, 1H, 3-*H*), 6.66 (d, 1H, *J*=7.8 Hz, 6-*H*), 6.62 (d, 1H, *J*=8.0 Hz, 5-***H***), 5.05 (s, 2H, $-OCH_2$), 2.25 (s, 3H, $-CH_3$) ppm. MS *m*/*z* (EI, 70 eV): 213 (M^+), 167, 122 (100), 104, 94, 91, 77, 65, 51. EA: Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.78; H, 7.14; N, 6.58.

***N*-Benzyl-2-benzyloxy-4-methyl-aniline (7a).** A 10 ml-flask was charged with iodobenzene (0.055 ml, 0.49 mmol), **6** (114 g, 0.535 mmol), sodium *tert*-butoxide (60 mg, 0.625 mmol), $Pd_2(DBA)_3$ (8 mg, Pd, 4% equiv.), BINAP (8 mg, 0.026 mmol), 18-C-6 (116 mg, 0.63 mmol), THF (1 ml). The mixture was warmed at 40°C for 48 h under vigorous stirring. After the reaction was completed, the solution was cooled to room temperature. The residue after evaporation of the solvent was purified by flash chromatography (Ethyl acetate:Petroleum ether=5:1) to give **7a** (132 mg, 93%). FT-IR (KBr): 3418, 3034, 2919, 2863, 1600, 1525, 1455, 1258, 1127, 746, 695 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.34–7.45 (m, 5H, Bn-*H*), 7.25 (m, 3H), 7.12 (m, 2H), 6.91 (dd, 1H, *J*=7.3, 1.0 Hz, 5-*H*), 6.81 (d, 1H, *J*=1.3 Hz, 6-*H*), 6.06 (s, 1H, N–*H*), 5.10 (s, 2H, $-CH_2$), 2.31 (s, 3H,$-CH_3$) ppm. MS *m*/*z* (EI, 70 eV): 289 (M^+), 271, 198 (100), 183, 170, 154, 143, 128, 115, 91, 77, 65, 51. HRMS Calcd for $C_{20}H_{19}NO(M^+)$: 289.1468, Found 289.1478.

1-Benzyloxy-3-methyl-9-H-carbazole (8a). To a stirred solution of **7a** (84 mg, 0.29 mmol) in HOAc (5 ml) was added $Pd(OAc)_2$ (98 mg, 0.44 mmol). The mixture was refluxed for 1 h under vigorous stirring. After the reaction was completed, the solution was cooled to room temperature. Then the HOAc was removed in vacuo and the residue was purified by flash chromatography (Ethyl acetate: Petroleum ether=10:1) to give **8a** as a yellow oil (25 mg, 32%). FT-IR (KBr): 3429, 3034, 2922, 2862, 1588, 1504, 1455, 1305, 1233, 1130, 1026, 748, 732 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.22 (1H, N–*H*), 8.02 (d, 1H, *J*=7.7 Hz), 7.20–7.80 (m, 10H, Ar-*H*), 6.83 (s, 1H, Ar-*H*), 5.24 (s, 2H, $-CH_2$), 2.53 (s, 3H, $-CH_3$) ppm. MS *m*/*z* (EI, 70 eV): 287 (M^+), 271, 258, 196 (100), 180, 168, 154, 139, 105, 91, 77, 65, 51. HRMS Calcd for $C_{20}H_{17}NO$ (M^+): 287.1311, Found 287.1305.

1-Hydro-3-methyl-9-H-carbazole (9). To a suspension of **8a** (70 mg, 0.24 mmol) in 95% ethanol (20 ml), 10% Pd/C (25 mg) was added. Hydrogenation of the mixture gave **9** by routine flash chromatography (Ethyl acetate:Petroleum ether=5:1) as a yellow solid (35 mg, 72.8%). FT-IR (KBr): 3464, 3412, 2922, 1615, 1587, 1500, 1454, 1298, 1227, 1118, 1091, 975, 766, 730 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.99 (d, 1H, *J*=7.9 Hz, 8-*H*), 7.46 (s, 1H, 2-*H*), 7.40 (d, 1H, *J*=10.0 Hz, 5-*H*), 7.36 (td, 1H, *J*=2.1 Hz, 7.8 Hz, 7-*H*), 7.19 (td, 1H, *J*=7.1 Hz, 1.7 Hz, 6-*H*), 6.64 (s, 1H, 4-*H*), 2.47 (s, 3H, $-CH_3$) ppm. MS *m*/*z* (EI, 70 eV): 197 (M^+, 100), 180, 168, 167, 154, 139, 128, 115, 99, 89, 76, 71, 63, 51, 43. EA: Calcd for $C_{13}H_{11}NO$: C, 79.17; H, 5.62; N, 7.10. Found: C, 78.72; H, 5.39; N, 7.46.

1,1′-Dihydroxy-3,3′-dimethyl-2,2′-biscarbazole (1). A solution of **9** (100 mg, 0.51 mmol) in chlorobenzene (10 ml) and di-*tert*-butyl peroxide (140 μl, 0.76 mmol) was refluxed for 2 h under air atmosphere. After cooling, the solvent was evaporated in vacuo and the remaining solid was purified by chromatography on silica gel with Ethyl acetate:Petroleum ether (3:1) as the eluant to give **1** as a yellow solid (92 mg, 95%). Mp >260°C. FT-IR (KBr): 3511, 3412, 2952, 2854, 1611, 1562, 1447, 1253, 1224, 745 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.09 (d, 1H, *J*=7.7 Hz), 7.61 (s, 2H), 7.59 (m, 2H), 7.39 (m, 2H), 7.18 (td, 2H, *J*=7.4, 1.0 Hz), 3.31 (b, 4H, N–*H*, O-*H*), 2.12 (s, 6H) ppm. MS *m*/*z* (EI, 70 eV): 392 (M^+), 386, 359, 330, 291, 262, 234, 196, 165, 130, 110, 91, 55, 44. HRMS Calcd for $C_{26}H_{20}N_2O_2$ (M^+): 392.1256, Found 392.1514. UV(Ethanol): 295.2, 253.6, 224.8 nm.

Resolution of (±)-1. To a mixture of **1** (60 mg, 0.153 mmol) and triethylamine (0.6 ml) in CH_2Cl_2 (10 ml) was added (+)-camphorsulfonyl (115 mg, 0.459 mmol), and the mixture was refluxed for 2 h. Then the mixture was treated with water (20 ml), extracted with CH_2Cl_2 (2×20 ml). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (silica gel, CH_2Cl_2:$CHCl_3$:Et_2O=50:1:2) provided **1b** (58 mg, 46%) and **1a**, respectively both as a white solid (60 mg, 48%). **1a**: mp 177–179°C. FT-IR (KBr): 3418, 2952, 2858, 1749, 1615, 1496, 1453, 1359, 1245, 1175, 746 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.90 (2H, N–*H*), 8.04 (d, 2H, *J*=7.8 Hz), 7.96 (s, 2H), 7.46 (m, 4H), 7.25 (m, 2H), 3.48 (d, 2H, *J*=14.8 Hz), 2.23 (d, 2H, *J*=14.8 Hz), 2.31 (s, 6H), 1.2–2.1 (m, 14H), 0.64 (s, 6H), 0.31 (s, 6H) ppm. MS *m*/*z* (EI, 70 eV): 823, 822, 757, 606, 542, 392 (100), 373, 330, 196, 109, 81. HRMS Calcd for $C_{46}H_{48}N_2O_8S_2$ (M^+): 820.1954, Found 820.2887. UV (Ethanol): 300, 252.4, 220.4 nm. $[\alpha]_D^{20}$=+3.75° (*c* 0.1, $CHCl_3$). **1b**: mp 132–134°C. FT-IR (KBr): 3420, 2962, 1749, 1615, 1497, 1454, 1363, 1246, 1172, 748 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.94 (2H, N–*H*), 8.05 (d, 2H, *J*=7.8 Hz), 7.98 (s, 2H), 7.45 (m, 4H), 7.27 (m, 2H), 3.13 (d, 2H, *J*=14.9 Hz), 2.53 (d, 2H, *J*=14.8 Hz), 2.34 (s, 6H), 0.88–2.27 (m, 14H), 0.50 (s, 6H), 0.41 (s, 6H) ppm. MS *m*/*z* (EI, 70 eV): 822, 757, 606, 542, 392 (100), 373, 330, 196, 109, 81. HRMS Calcd for $C_{46}H_{48}N_2O_8S_2$ (M^+): 820.1954, Found 820.2812. UV (Ethanol): 298.8, 254.6, 220.8 nm. $[\alpha]_D^{20}$=+15.2° (*c* 0.48, $CHCl_3$).

(+)-1,1′-Dihydroxy-3,3′-dimethyl-2,2′-biscarbazole (a*R*-1). To a mixture of **1a** (20 mg, 0.024 mmol) in EtOH–H_2O (1:1, 30 ml) was added KOH (80 mg, 1.43 mmol) at room temperature. When TLC showed no starting material left, the mixture was extracted with CH_2Cl_2 (3×20 ml). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the

residue by flash chromatography (silica gel, Ethyl acetate: Petroleum ether=2:1) provided (+)-**1** as a white solid (7 mg, 73.2%). Mp>260°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (b, 2H, N–*H*), 8.09 (d, 2H, *J*=8.0 Hz), 7.70 (s, 2H), 7.43 (m, 4H), 7.26 (m, 2H), 2.17 (s, 6H) ppm. FT-IR (KBr): 3508, 3409, 2922, 1614, 1564, 1251 nm. MS *m/z* (EI, 70 eV): 392, 391 (100), 197, 196. HRMS Calcd for $C_{26}H_{20}N_2O_2$ (M^+): 392.1526, found 392.1513. UV (Ethanol): 296.4, 252.4, 224.4 nm. $[\alpha]_D^{20}=+29.9°$ (*c* 0.67, $CHCl_3$).

(−)-1,1′-Dihydroxy-3,3′-dimethyl-2,2′-biscarbazole (a*S*-1). To a mixture of **1b** (20 mg, 0.024 mmol) in EtOH/H_2O (1:1, 30 ml) was added KOH (100 mg) at room temperature. The stirring was kept until the disappearance of the starting material on TLC. The products were extracted with CH_2Cl_2 (3×20 ml). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (silica gel, Ethyl acetate:Petroleum ether=2:1) provided (−)-**1** as a white solid (9 mg, 94%). Mp>260°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (b, 2H, N–H), 8.09 (d, 2H, *J*=8.0 Hz), 7.71 (s, 2H), 7.47 (m, 4H), 7.26 (m, 2H), 2.18 (s, 6H) ppm. FT-IR (KBr): 3510, 3422, 2925, 1615, 1564, 1253 nm. MS *m/z* (EI, 70 eV): 392, 391 (100), 197, 196. HRMS Calcd for $C_{26}H_{20}N_2O_2$ (M^+): 392.1526, found 392.1531. UV (Ethanol): 295.2, 253.6, 224.8 nm. $[\alpha]_D^{20}=-39°$ (*c* 0.1, $CHCl_3$).

4-Methyl-cyclohexane-1,2-dione-1-(4′-methoxy)-phenylhydrazone (11a). To a stirred solution of sodium acetate (22 g, 27 mmol) in H_2O (15 ml) was added **10** (1.4 g, 10 mmol) in methanol (29 ml). The solution was kept for the next step. Another 50 ml-flask charged with 4-methoxyaniline (1.42 g, 11.5 mmol), ice (5 g), water (5 g), 12N HCl (4.8 ml) was cooled to 0°C, and then sodium nitrite (0.8 g, 11.5 mmol) in water (10 ml) was added. The mixture was stirred for 25 min at this temperature, then stirred under room temperature for another 15 min. The solution above was added slowly, and the mixture was stirred for 30 min, filtrated, washed by water. The red solid was dried and recrystallized from ethanol to give **11a** as red solid (1.33 g, 54%). Mp 203–204°C. FT-IR (KBr): 3243, 2926, 1658, 1600, 1488, 1420, 1219, 1038, 831, 724 cm^{-1}. MS *m/z* (EI, 70 eV): 246 (M^+), 229, 175, 135, 122, 108, 95, 77, 69, 55, 42. EA: Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37, Found: C, 68.06; H, 7.35; N, 11.35.

1-Oxo-3-methyl-6-methoxy-1,2,3,4-tetrahydrocarbazole (12). A 25 ml-flask was charged with 11a (1.23 g, 5.37 mmol), HOAc (9 ml), 12N HCl (3 ml), and the mixture was refluxed for 10 min. Water (60 ml) was added slowly while cooling the mixture. The yellow solid was gained after filtrating, then washed with water and dried over infrared lamp. The yellow solid was recrystallized from benzene to give yellow solid **12** (560 mg, 44.2%). Mp 200–203°C. FT-IR (KBr): 3251, 2953, 1653, 1537, 1484, 1447, 1216, 1139, 1029, 808 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.05 (s, 1H), 7.34 (m, 1H), 7.04 (m, 2H), 3.87 (s, 3H, –OC*H*$_3$), 3.11 (dd, 1H, *J*=5.3, 3.0 Hz), 2.53 (m, 4H), 1.23 (d, 3H, *J*=5.9 Hz, –C*H*$_3$) ppm. MS *m/z* (EI, 70 eV): 229 (M^+), 214, 201, 186, 170, 159, 144, 129, 116, 103, 89, 77, 69, 51, 42. EA: Calcd for $C_{14}H_{13}NO_3$: C, 73.33; H, 6.60; N, 6.11. Found: C, 72.83; H, 6.29; N, 6.10.

1-Hydroxy-3-methyl-6-methoxy-carbazole (13). A 25 ml-flask was charged with **12** (700 mg, 3.06 mmol), 10% Pd/C (450 mg), biphenyl ether (30 ml), 1,2,4-trimethylbenzene (3.5 ml), and the mixture was warmed at 200~220°C for 12 h in vacuo. Then the mixture was cooled to room temperature, and the product was purified by flash chromatography (Ethyl acetate:Petroleum ether=20:1, then CH_2Cl_2/HCOOH=100:0.1) provided **13** as a yellow solid (504 mg, 73%). FT-IR (KBr): 3429, 3282, 2911, 1622, 1591, 1506, 1482, 1288, 1206, 1178, 1143, 832, 761 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47 (d, 1H, *J*=2.4 Hz, 5-*H*), 7.40 (s, 1H, 4-*H*), 7.27 (d, 1H, *J*=8.7 Hz, 8-*H*), 7.06 (dd, 1H, *J*=8.8, 2.4 Hz, 7-*H*), 6.60 (s, 1H, 2-*H*), 5.00 (b, 2H, N–*H*, O–*H*), 3.91 (s, 3H, –OC*H*$_3$), 2.46 (s, 3H, –C*H*$_3$) ppm. MS *m/z* (EI, 70 eV): 227 (M^+, 100), 212, 198, 184, 166, 155, 140, 128, 113, 91, 77, 63. HRMS Calcd for $C_{14}H_{13}NO_2$(M^+): 227.0947, found 227.0947.

1,1′-Dihydroxy-3,3′-dimethyl-6,6′-methoxy-2,2′-biscarbazole (2). A solution of **13** (100 mg, 0.44 mmol) in chlorobenzene (10 ml) and di-*tert*-butyl peroxide (122 μl, 0.66 mmol) was refluxed for 2 h under air atmosphere. After cooling, the solvent was evaporated in vacuo and the remaining solid was purified by chromatography on silica gel with Ethyl acetate:Petroleum ether (3:1) as the eluant to give **2** as a yellow solid (75 mg, 79.3%). Mp >260°C. FT-IR (KBr): 3518, 3406, 2924, 1621, 1564, 1496, 1300, 1211, 1154, 1031, 779 cm^{-1}. ^{1}H NMR (400 MHz, D-acetone): δ 7.64 (d, 2H, *J*=2.4 Hz, 5-*H*), 7.57 (d, 2H, *J*=0.8 Hz, 4-*H*), 7.48 (dd, 2H, *J*=8.8 Hz, 0.3 Hz, 8-*H*), 7.04 (dd, 2H, *J*=8.7, 2.5 Hz, 7-*H*), 3.91 (s, 6H, –OC*H*$_3$), 3.02 (s, 4H, N–*H*, O-*H*), 2.10 (s, 3H, –C*H*$_3$) ppm. MS *m/z* (EI, 70 eV): 452 (M^+), 437, 419, 376, 333, 292, 250, 226, 211, 197, 160, 139. HRMS Calcd for $C_{28}H_{24}N_2O_4$: 452.1737, Found: 452.1738.

Resolution of (±)-2. To a mixture of **2** (50 mg, 0.11 mmol) and triethylamine (0.5 ml) in CH_2Cl_2 (10 ml) was added (+)-camphorsulfonyl (84 mg, 0.33 mmol), and the mixture was refluxed for 2 h. Then the mixture was treated with water (20 ml), extracted with CH_2Cl_2 (2×15 ml). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (silica gel, CH_2Cl_2:$CHCl_3$:Et_2O=50:1:2) provided **2b** (47 mg, 48.3%) and **2a**, respectively, both as a white solid (40 mg, 41%). **2a**: mp 235–237°C. FT-IR (KBr): 3413, 2956, 2925, 1748, 1585, 1496, 1466, 1360, 1291, 1212, 800 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.76 (2H, N–*H*), 7.91 (s, 2H, 4-*H*), 7.50 (d, 2H, *J*=2.4 Hz, 5-*H*), 7.38 (d, 2H, *J*=8.8 Hz, 8-*H*), 7.09 (dd, 2H, *J*=8.8, 2.6 Hz, 7-*H*), 3.93 (s, 6H, –OC*H*$_3$), 3.47 (d, 2H, *J*=14.9 Hz), 2.25 (d, 2H, *J*=14.9 Hz), 2.29 (s, 6H), 1.2–2.1 (m, 14H), 0.64 (s, 6H), 0.33 (s, 6H) ppm. MS *m/z* (EI, 70 eV): 882, 881, 817, 753, 667, 602, 452 (100), 397, 333, 226, 152, 109, 81. HRMS Calcd for $C_{48}H_{52}N_2O_8S_2$ (M^+): 880.3065, Found 880.3068. $[\alpha]_D^{20}=+38.1°$ (*c* 1.08, $CHCl_3$). **2b**: mp 203–204°C. FT-IR(KBr): 3412, 2956, 2925, 1748, 1585, 1496, 1466, 1364, 1291, 1212, 802 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.78 (2H, N–*H*), 7.94 (s, 2H, 4-*H*), 7.51 (d,

2H, *J*=2.4 Hz, 5-*H*), 7.37 (d, 2H, *J*=8.8 Hz, 8-*H*), 7.09 (dd, 2H, *J*=8.8, 2.5 Hz, 7-*H*), 3.93 (s, 6H, –OC*H*$_3$), 3.13 (d, 2H, *J*=14.8 Hz), 2.53 (d, 2H, *J*=14.9 Hz), 2.32 (s, 6H), 1.2–2.1 (m, 14H), 0.51 (s, 6H), 0.42 (s, 6H) ppm. MS *m*/*z* (EI, 70 eV): 882, 881, 817, 753, 667, 602, 452 (100), 392, 301, 226, 152, 109, 95. HRMS Calcd for $C_{48}H_{52}N_2O_8S_2$ (M^+): 880.3065, Found 880.3065. $[\alpha]_D^{20}=-34.9°$ (*c* 1.14, $CHCl_3$).

(+)-1,1′-Dihydroxy-3,3′-dimethyl-6,6′dimethoxy-2,2′-biscarbazole (a*R*-2). To a mixture of **2a** (21 mg, 0.024 mmol) in 95% EtOH (30 ml) was added KOH (100 mg) at room temperature. The accomplishment of the hydrolysis was monitored by TLC, then the products were extracted with CH_2Cl_2 (3×20 ml). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (silica gel, Ethyl acetate:Petroleum ether=2:1) provided (+)-**2** as a white solid (6 mg, 57%). Mp>260°C. ^{1}H NMR(300 MHz, $CDCl_3$) 8.13 (b, 2H, N–*H*), 7.66 (s, 2H), 7.55 (d, 2H, *J*=2.4 Hz), 7.40 (d, 2H, *J*=8.8 Hz), 7.11 (dd, 2H, *J*=8.8, 2.4 Hz), 5.12 (s, 2H, O-*H*), 3.96 (s, 6H, –OC*H*$_3$), 2.17 (s, 3H, –C*H*$_3$). FT-IR (KBr): 3529, 3414, 2924, 1622, 1564, 1212. UV (Ethanol): 302.0, 254.0, 226.0, 203.2 nm. MS *m*/*z* (EI, 70 eV): 453, 452 (M^+), 227, 226. HRMS Calcd for $C_{28}H_{24}N_2O_4$ (M^+): 452.1737, found 4520.1738. $[\alpha]_D^{20}=+44.3°$ (*c* 0.09, $CHCl_3$).

(−)-1,1′-Dihydroxy-3,3′-dimethyl-6,6′dimethoxy-2,2′-biscarbazole (a*S*-2). To a mixture of **2b** (28 mg, 0.032 mmol) in EtOH–H_2O (1:1, 30 ml) was added KOH (500 mg) at room temperature. When TLC showed no starting material was left, the products were extracted with CH_2Cl_2 (3×20 ml). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (silica gel, Ethyl acetate:Petroleum ether=2:1) provided (−)-**2** as a white solid (13 mg, 90%). Mp>260°C. ^{1}H NMR (400 MHz, $CDCl_3$) 8.10 (b, 2H, N–*H*), 7.65 (s, 2H), 7.55 (d, 2H, *J*=2.4 Hz), 7.39 (d, 2H, *J*=8.7 Hz), 7.10 (dd, 2H, *J*=8.8, 2.5 Hz), 3.95 (s, 6H, –OC*H*$_3$), 2.17 (s, 3H, –C*H*$_3$). FT-IR(KBr): 3520, 3412, 2924, 1561, 1465, 1213. UV (Ethanol): 302.0, 253.6, 226.8, 203.6 nm. MS *m*/*z* (EI, 70 eV): 453, 452 (M^+), 227, 226. HRMS Calcd for $C_{28}H_{24}N_2O_4$ (M^+): 452.1737, found 4520.1738. $[\alpha]_D^{20}=-44.7°$ (*c* 0.13, $CHCl_3$).

***N*-(3′,5′-Dimethoxy)-benzyl-2-benzyloxy-4-methyl-aniline (7b).** A 10 ml-flask was charged with 2,4-dimethoxy-iodobenzene (132 mg, 0.5 mmol), **6** (128 g, 0.6 mmol), sodium *tert*-butoxide (67 mg, 0.7 mmol), $Pd_2(DBA)_3$ (10 mg, Pd, 4% equiv.), BINAP (9 mg, 0.026 mmol), 18-C-6 (116 mg, 0.63 mmol), THF (1 ml). The mixture was warmed at 40°C for 48 h under vigorous stirring. After the reaction was completed, the solution was cooled to room temperature. The residue after evaporation of the solvent was purified by flash chromatography (Ethyl acetate:Petroleum ether=5:1) to give **7b** (96 mg, 77%). FT-IR (KBr): 3421, 2938, 2834, 1618, 1528, 1509, 1465, 1280, 1258, 1208 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32–7.47 (m, 5H, Bn-*H*), 7.22 (d, 1H, *J*=8.3 Hz, 4-*H*), 7.06 (d, 1H, *J*=7.7 Hz, 3-*H*), 6.76 (s, 1H, 1-*H*), 6.68 (d, 1H, *J*=8.0 Hz, 2-*H*), 6.51 (d, 1H, *J*=2.3 Hz, 6-H), 5.11 (s, 2H, –C*H*$_2$), 3.80 (s, 3H, –OC*H*$_3$), 3.79 (s, 3H, –OC*H*$_3$), 2.28 (s, 3H, C*H*$_3$) ppm. MS *m*/*z* (EI, 70 eV): 350, 349 (M^+, 100), 291, 258, 243, 227, 212, 184, 144, 110, 91, 77, 65, 52. HRMS Calcd for $C_{22}H_{23}NO_3$ (M^+): 349.1679, Found 349.1668.

4-Methyl-cyclohexane-1,2-dione-1-(3′,5′-dimethoxy)-phenylhydrazone (11b). To a stirred solution of sodium acetate (4.4 g, 54 mmol) in H_2O (15 ml) was added **10** (2.8 g, 20 mmol) in methanol (29 ml). The solution was kept for the next step. Another 50 ml-flask charged with 3,5-dimethoxylaniline (3.52 g, 25 mmol), ice (5 g), water (5 g), 12N HCl (9.5 ml) was cooled to 0°C, and then sodium nitrite (1.6 g, 23 mmol) in water (10 ml) was added. The mixture was stirred for 25 min at this temperature, then stirred under room temperature for another 15 min. The solution above was added slowly, and the mixture was stirred for 30 min, filtrated, washed by water. The red solid was dried and recrystallized from ethanol to give **11b** as red solid (4.02 g, 72.5%). Mp 91–93°C. FT-IR (KBr): 2929, 1620, 1517, 1497, 1208, 1164, 1026 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 14.0(1H, N–*H*), 7.53 (d, 1H, *J*=8.2 Hz), 6.49 (m, 2H), 3.89 (s, 3H, –OC*H*$_3$), 3.79 (s, 3H, –OC*H*$_3$), 2.69 (m, 3H), 2.04 (m, 3H), 1.46 (m, 1H), 1.04 (d, 3H, *J*=6.6 Hz, –C*H*$_3$) ppm. MS *m*/*z* (EI, 70 eV): 276 (M^+), 261, 165, 152 (100), 138, 124, 109, 93, 79, 69, 55, 42. EA: Calcd for $C_{15}H_{20}N_2O_3$: C, 65.22; H, 7.25; N, 10.14. Found: C, 65.26; H, 7.47; N, 10.11.

Toluene-4-sulfonic acid 2-amino-5-methyl-phenyl ester (15). To a suspension of 2-amino-5-methylphenol (2.66 g, 20 mmol) in CH_2Cl_2 (40 ml) cooled to 0°C, triethylamine (2.78 ml, 20 mmol) and *p*-tosyl chloride (3.81 g, 20 mmol) were added with stirring. When TLC showed no starting material left, the products were quenched with water (30 ml) and the aqueous layer was extracted with CH_2Cl_2 (3×20 ml). The combined organic layers were dried over Na_2SO_4, filtered, and the solvent was removed in vacuo. The residue was purified by recrystallization from ether to give **15** as a yellow solid (4.27 g, 77%). Mp 81–82°C. FT-IR (KBr): 3482, 3389, 3035, 2919, 1740, 1630, 1597, 1521, 1198, 1089 cm^{-1}. ^{1}H NMR (90 MHz, $CDCl_3$): δ 7.85 (d, 2H, *J*=9.0 Hz), 7.32 (d, *J*=9.0 Hz, 2H), 6.62–6.91 (m, 3H), 3.96 (2H, –N*H*$_2$), 2.50 (s, 3H, C*H*$_3$), 2.22 (s, 3H, –C*H*$_3$) ppm. MS *m*/*z* (EI, 70 eV): 278, 277 (M^+), 213, 198, 185, 170, 155, 122 (100), 107, 94, 77, 65, 51, 42. EA: Calcd for $C_{14}H_{15}NSO_3$: C, 60.63; H, 5.46; N, 5.05. Found: C, 60.51; H, 5.39; N, 5.24.

Toluene-4-sulfonic acid 2-amino-3-bromo-5-methyl-phenyl ester (16). To a stirred solution of **15** (1.369 g, 4.94 mmol), in DMSO (15 ml) was added 15 ml 48% aqueous HBr. Heat was applied after stirring for 24 h at room temperature. The reaction progress was monitored by TLC analysis. Then the reaction mixture was diluted with water and made basic (pH=10) by slow addition of solid NaOH. The aqueous layer was extracted with ether (3×30 ml) and the combined organic layers were washed by brine, dried over Na_2SO_4. The solvent was removed in vacuo and the residue purified by flash chromatography (silica gel, Ethyl acetate:Petroleum ether=5:1) to give **16** as a white solid (1.41 g, 80%). Mp 134–135°C. FT-IR(KBr): 3475, 3389, 2928, 1629, 1596, 1495, 1365, 1177, 1091 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79 (d,

2H, J=8.3 Hz), 7.32 (d, 2H, J=8.1 Hz), 7.13 (d, 1H, J=1.0 Hz), 6.67 (d, 1H, J=1.1 Hz), 3.79 (b, 2H, –NH_2), 2.47 (s, 3H, –CH_3), 2.14 (s, 3H, –CH_3) ppm. MS *m*/*z* (EI, 70 eV): 358, 357, 356 (M^+), 355, 241, 214, 202 (100), 184, 174, 172, 155, 134, 120, 93, 65. HRMS Calcd for $C_{24}H_{25}NO_5$ (M^+): 407.1734, Found 407.1729.

Toluene-4-sulfonic acid 2-amino-3′,5′-dimethoxy-5-methyl-biphenyl-3-yl ester (18a). A 25 ml-flask was charged $Pd(PPh_3)_4$ (20 mg, 0.017 mmol), benzene (15 ml), **16** (180 mg, (0.5 mmol) and aqueous solution of Na_2CO_3 (2 ml of 2 M, 4 mmol), then 3,5-dimethoxy-phenylboronic acid (110 mg, 0.6 mmol) in ethanol (4 ml) was added. The mixture was refluxed for 8 h under vigorous stirring. After the reaction was completed, the solution was cooled to room temperature. The product was extracted with ether, washed by brine, and finally dried over Na_2SO_4. The residue after evaporation of the solvent was purified by flash chromatography (Ethyl acetate:Petroleum ether=5:1) to give 18a (204 mg, 99%). Mp 122–123°C. FT-IR (KBr): 3498, 3406, 2941, 1629, 1588, 1366, 1205, 1154, 1089, 1062, 775 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.82 (d, 2H, J=8.3 Hz), 7.35 (d, 2H, J=8.1 Hz), 6.84 (s, 1H), 6.75 (s, 1H), 6.47 (d, J=2.0 Hz, 1H), 6.44 (d, J=2.1 Hz, 1H), 6.04 (dd, J=8.0, 2.0 Hz, 1H), 3.79 (s, 6H, –OCH_3), 3.74 (s, 2H, –NH_2), 2.47 (s, 3H, –CH_3), 2.20 (s, 3H, –CH_3) ppm. MS *m*/*z* (EI, 70 eV): 414, 413 (M^+), 374, 277, 258(100), 243, 227, 212, 184, 154, 122, 111, 91, 77, 42. HRMS Calcd for $C_{22}H_{23}NSO_5$ (M^+): 413.1298, Found 413.1295.

Toluene-4-sulfonic acid 2-amino-2′-bromo-3′,5′-dimethoxy-5-methyl-biphenyl-3-yl ester (19). To a stirred solution of **18a** (150 mg, 0.36 mmol), in DMSO (5 ml) was added 2 ml 48% aqueous HBr at room temperature for 4 days. Then the reaction mixture was diluted with water and made basic (pH=10) by slow addition of solid NaOH. The aqueous layer was extracted with ether (3×30 ml) and the combined organic layers were washed by brine, dried over Na_2SO_4. The solvent was removed in vacuo and the residue purified by flash chromatography (silica gel, Ethyl acetate:Petroleum ether=5:1) to give **19** as a white solid (142 mg, 79.5%). Mp 140–141°C. FT-IR (KBr): 3452, 3368, 2939, 1584 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.79 (d, 2H, J=8.4 Hz), 7.31 (d, 2H, J=7.3 Hz), 6.94 (d, 1H, J=2.32 Hz), 6.72 (d, 1H, J=2.01 Hz), 6.48 (d, 1H, J=2.73 Hz), 6.37 (d, 1H, J=2.85 Hz), 3.89 (s, 6H, –OCH_3), 3.78 (s, 2H, –NH_2), 2.44 (s, 3H, –CH_3), 2.23 (s, 3H, –CH_3) ppm. MS *m*/*z* (EI, 70 eV): 494, 492, 412, 337, 257(100), 242. HRMS Calcd for $C_{22}H_{22}NBrSO_5$ (M^+): 491.0402, Found 491.0403.

Toluene-4-sulfonic acid 6,8-dimethoxy-3-methyl-9H-carbazole-1-yl ester (20). A solution of $Pd(PPh_3)_4$ (704 mg, 0.6 mmol), toluene (10 ml), **19** (250 mg, 0.5 mmol), Na_2CO_3 (65 mg) were refluxed for 6 h. The mixture was cooled and the solvent was removed in vacuo. The residue was purified by flash chromatography to give the product **20** as a white solid (188 mg, 90%). Mp 152–154°C. FT-IR (KBr): 3384, 2920, 1596 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.82 (s, 1H, –NH), 7.77 (d, 2H, J=8.4 Hz), 7.65 (s, 1H), 7.29 (d, 1H, J=8.8 Hz), 7.01 (d, 1H, J=2.0 Hz), 6.70 (d, 1H, J=0.8 Hz), 6.57 (d, 1H, J=2.1 Hz), 3.96 (s, 3H, –OCH_3), 3.90 (s, 3H), 2.42 (s, 3H, –CH_3), 2.38 (s, 3H, –CH_3) ppm. MS *m*/*z* (EI, 70 eV): 412, 256, 232, 226, 213, 198. HRMS Calcd for $C_{22}H_{21}NSO_5$ (M^+): 411.1141, Found 411.1137.

6,8-Dimethoxy-3-methyl-9H-carbazole-1-OH (21). A mixture of **20** (36 mg, 0.09 mmol) and NaOH (98 mg) in water (5 ml) and ethanol (5 ml) was stirred under reflux for 1 h. The mixture was quenched with water (10 ml). After extractive work up (CH_2Cl_2, 3×30 ml), the combined organic layers were washed by brine and dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (silica gel, Ethyl acetate:Petroleum ether=5:1) provided **21** as a yellow solid (20 mg, 88%). Mp 181–182°C. FT-IR (KBr): 3518, 3380, 1588, 1512 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.27 (s, 1H, –NH), 7.40 (s, 1H), 7.06 (d, 1H, J=1.9 Hz), 6.64 (s, 1H), 6.57 (d, 1H, J=2.0 Hz), 5.36 (s, 1H, –OH), 3.97 (s, 3H, –OCH_3), 3.92 (s, 3H), 2.46 (s, 3H, –CH_3) ppm. MS *m*/*z* (EI, 70 eV): 257, 242, 226, 214, 199. EA: Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.32; H, 6.03; N, 5.29.

Clausenamine-A (3). A solution of **21** (80 mg, 0.31 mmol) in chlorobenzene (10 ml) and di-*tert*-butyl peroxide (86 μl, 0.45 mmol) was refluxed for 2 h under air atmosphere. After cooling, the solvent was evaporated in vacuo and the remaining solid was purified by chromatography on silica gel with Ethyl acetate:Petroleum ether (3:1) as the eluant to give **3** as a yellow solid (72 mg, 90%). FT-IR (KBr): 3493, 3404, 1596 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.76 (s, 2H, –NH), 7.59 (s, 2H), 7.02 (s, 2H), 6.43 (s, 2H), 5.83 (s, 2H, –OH), 3.90 (s, 6H, –OCH_3), 3.56 (s, 6H), 2.14 (s, 6H, –CH_3) ppm. MS *m*/*z* (EI, 70 eV): 512, 497, 482, 449, 255. HRMS Calcd for $C_{30}H_{28}N_2O_6$ (M^+): 512.1948, Found 512.1974.

Resolution of (±)-3. To a mixture of **3** (14 mg, 0.027 mmol) and triethylamine (0.25 ml) in CH_2Cl_2 (10 ml) was added (+)-camphorsulfonyl (13 mg, 0.052 mmol), and the mixture was refluxed for 2 h. Then the mixture was treated with water (20 ml), extracted with CH_2Cl_2 (2×15 ml). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (silica gel, CH_2Cl_2:$CHCl_3$:Et_2O=50:1:2) provided **3b** (12 mg, 47%) and **3a** respectively both as a white solid (12 mg, 47%). **3a**: mp 167–168°C. FT-IR (KBr): 3434, 2924, 1749 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.75 (s, 2H, –NH), 7.88 (s, 2H), 7.06 (d, 2H, J=1.8 Hz), 6.60 (d, 2H, J=1.9 Hz), 3.95 (s, 6H, –OCH_3), 3.93 (s, 6H, –OCH_3), 3.43 (d, 2H, J=14.8 Hz), 2.17 (d, 2H, J=14.8 Hz), 2.36 (s, 6H), 0.8–1.9 (M, 14H), 0.61 (s, 6H), 0.30 (s, 6H) ppm. MS *m*/*z* (EI, 70 eV): 942, 940, 878, 876, 727, 663, 512. HRMS Calcd for $C_{50}H_{56}N_2S_2O_{12}$ (M^+): 940.3271, Found 940.3151. **3b**: mp 148–150°C. FT-IR (KBr): 3431, 2924, 1749 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.75 (s, 2H, –NH), 7.90 (s, 2H), 7.07 (d, 2H, J=1.9 Hz), 6.60 (d, 2H, J=2.0 Hz), 3.96 (s, 6H, –OCH_3), 3.93 (s, 6H, –OCH_3), 3.08 (d, 2H, J=14.8 Hz), 2.48 (d, 2H, J=14.9 Hz), 2.32 (s, 6H), 0.8–2.2 (M, 14H), 0.49 (s, 6H), 0.40 (s, 6H) ppm. MS *m*/*z* (EI, 70 eV): 942, 878, 813, 727, 663, 512. HRMS Calcd for $C_{50}H_{56}N_2S_2O_{12}$ (M^+): 940.3271, Found 940.3344.

(+)-Clausenamine-A (3). The mixture of **3a** (35 mg, 0.037 mmol) in EtOH–H_2O (1:1, 30 ml) and KOH (100 mg) was kept stirring at room temperature until no starting material was left, the products were extracted with CH_2Cl_2 (3×20 ml). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (silica gel, Ethyl acetate:Petroleum ether=2:1) provided (+)-**3** as a white solid (16 mg, 84%). FT-IR (KBr): 3398, 2932, 1595 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.69 (s, 2H, –NH), 7.60 (s, 2H, -4H), 7.04 (d, 2H, J=1.7 Hz, -5H), 6.45 (d, 2H, J=1.6 Hz, -7H), 5.73 (s, 2H, –OH), 3.91 (s, 6H, –OCH_3), 3.63 (s, 6H), 2.15 (s, 6H, –CH_3) ppm. MS *m*/*z* (EI, 70 eV): 512, 497, 482, 449, 256. HRMS Calcd for $C_{30}H_{28}N_2O_6$ (M^+): 512.1948, Found 512.1970. $[\alpha]_D^{21}$=+142.2° (*c* 0.75, $CHCl_3$).

(−)-Clausenamine-A (3). To a mixture of **3b** (37 mg, 0.037 mmol) in EtOH–H_2O (1:1, 30 ml) was added KOH (100 mg) at room temperature. The accomplishment of the hydrolysis was monitored by TLC, then the products were extracted with CH_2Cl_2 (3×20 ml). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (silica gel, Ethyl acetate:Petroleum ether=2:1) provided (−)-**3** as a white solid (17 mg, 87%). FT-IR (KBr): 3400, 2935, 1595 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 9.12 (s, 2H, –NH), 7.59 (s, 2H, -4H), 6.95 (d, 2H, J=1.4 Hz, -5H), 6.38 (s, 2H, –OH), 6.30 (d, 2H, J=1.0 Hz, -7H), 3.87 (s, 6H, –OCH_3), 3.26 (s, 6H), 2.15 (s, 6H, –CH_3) ppm. MS *m*/*z* (EI, 70 eV): 512, 497, 482, 449, 256. HRMS Calcd for $C_{30}H_{28}N_2O_6$ (M^+): 512.1948, Found 512.1923. $[\alpha]_D^{21}$=−147.6° (*c* 0.65, $CHCl_3$).

Acknowledgements

We are grateful to the National Science Foundation of China (29772052) and the Chinese Academy of Science (KT951-A1-506-05) for financial support. We also thank Prof. John Pezzuto and Pamela Tamez at UIC in USA for the antimalarial bioassays.

References

1. (a). Furukawa, H.; Wu, T.-S.; Ohta, T. *Chem. Pharm. Bull.* **1983**, *31*, 4202–4205. (b). Ito, C.; Thoyama, Y.; Omura, M.; Kajiura, I.; Furukawa, H. *Chem. Pharm. Bull.* **1993**, *41*, 2906–2100. (c). Kapil, R.-S. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic; New York, 1971; Vol. 13, pp 271–302. (d). Wu, T.-S.; Ohta, T.; Furukawa, H. *Heterocycles* **1983**, *20*, 1267. (e). Furukawa, H.; Wu, T.S.; Ohata, T., Kuoh, C.-S. *Chem. Pharm. Bull.* **1985**, *33*, 4132–4138.

2. Wu, T.-S.; Humg, S.-C.; Wu, P.-L. *Tetrahedron. Lett.* **1996**, *37*, 7819–7822.

3. Bringmann, G.; Ledermann, A.; Holenz, J.; Kao, M.-T.; Busse, U.; Wu, H.-G.; Francois, G. *Planta. Med.* **1998**, *64*, 54–57.

4. Zhang, A.-M.; Lin, G.-Q. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1021–1023.

5. Lin, G.-Q.; Zhang, A.-M. *Tetrahedron. Lett.* **1999**, *40*, 341–344.

6. Bringmann, G.; Ledermann, A.; Stahl, M.; Gulden, K.-P. *Tetrahedron* **1995**, *51*, 9353–9360.

7. (a) Hall, R. J.; Jackson, A. H.; Oliveira-Campes, A. M. F.; Queiroz, M.-J. R. P.; Shannon, P. V. R. *Heterocycles* **1990**, *3*, 401–405. (b) Hall, R. J.; Marcoux, J.-F.; Oliveira-Campes, A. M. F.; Queiroz, M.-J. R. P.; Shannon, P. V. R. *J. Chem. Soc., Perkin. Trans. 1* **1992**, 3439–3450. (c). Su, T.-L.; Kohler, B.; Chou, T.-C.; Chun, M. W.; Watanabe, K. A. *J. Med. Chem.* **1992**, *14*, 2703–2710. (d). Wagaw, S.; Buchwald, S.-L. *J. Org. Chem.* **1997**, *62*, 1568–1569. (e). Wolfe, J.-P.; Buchwald, S.-L. *J. Org. Chem.* **1997**, *62*, 6066–6068.

8. (a) Akermark, L.; Eberson, E.-J; Pettersson, E. *J. Org. Chem.* **1975**, *40*, 1365–1367. (b). Hewlins, J.-E; Michael Jackson, A.-H.; Long, A.; Ana, O.-C.; Shannon, P.-V.-P. *J. Chem. Res.* **1986**, 292–293.

9. Bringmann, G.; Ledermann, A.; Francios, G. *Heterocycles* **1995**, *40*, 293–300.

10. Chakraborty, D. P.; Chowdhury, B. K. *J. Org. Chem.* **1968**, *33*, 1265–1268.

11. Chakraborty, D. P.; Islam, A.; Bhattacharyya, P. *J. Org. Chem.* **1973**, *38*, 2728–2729.

12. (a) Murakami, Y.; Watanabe, T.; Takahashi, H.; Yokoo, H.; Nakazawa, Y.; Koshimizu, M.; Adachi, N.; Kurita, M.; Yoshino, T.; Inagaki, T.; Ohishi, M.; Watanabe, M.; Tani, M.; Yokoyama, Y. *Tetrahedron* **1998**, *54*, 45–64. (b) Ishii, H.; Murakami, Y.; Furuse, T.; Hosoya, K.; Ikeda, N. *Chem. Pham. Bull.* **1973**, *21*, 1495.

13. Kurija, K. *Chem. Ind. (London)* **1974**, 345.

14. Majetich, G.; Hicks, R.; Reister, S. *J. Org. Chem.* **1997**, *62*, 4321–4326.

15. Dol, G. C.; Kamer, P. C.; Leeuwen, P. W. N. M. *Eur. J. Org. Chem.* **1998**, 359–364.

16. Miller, R. B.; Dugar, S. *Organometallics* **1984**, *3*, 1261.

17. Miller, R. B.; Dugar, S. *Tetrahedron. Lett.* **1989**, *30*, 297–300.

18. (a) Boger, D. L.; Panek, J. S. *Tetrahedron. Lett.* **1984**, *25*, 3175–3178. (b) Wood, J. L.; Stoltz, B. M.; Dietrich, H. J.; Pflum, D. A.; Petsh, D. T. *J. Am. Chem. Soc.* **1997**, *119*, 9647–9051.

19. (a) Zhang, F.-J.; Lin, G.-Q.; Hung, Q.-C. *J. Org. Chem.* **1995**, *60*, 6427–6430. (b). Ng, M.-K.; Chow, H.-F.; Chan, T.-L.; Mak, T.-C. *Tetrahedron. Lett.* **1996**, *37*, 2979–2982. (c). Chow, H.-F., Wan, C.-W.; Ng, M.-K. *J. Org. Chem.* **1996**, *61*, 8712–8714.

20. Harada, N.; Nakanishi, K. *Circular Dichroic Spectroscopy-Exciton Coupling in Organic Stereochemistry*, University Science Books: Mill Valley, CA, 1983 (and also at Oxford University Press, Oxford).