Protecting-group-free synthesis of the bisindolylmaleimide GF109203X

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DOI: http://dx.doi.org/10.3998/ark.5550190.p008.950

Abstract

The bisindolylmaleimide GF109203X is a highly selective inhibitor to Protein Kinase C (PKC) and has attracted much attention. However, its reported synthesis required protecting groups. In order to achieve a short and N-protecting-group-free synthesis of GF109203X, an investigation on *N*-alkylation of arcyriarubin A was carried out using different bases, solvents and equivalents of bromododecane. It is found that mono-N-alkylation and mono-N'-alkylation could be achieved respectively. Thus, a protecting-group-free synthesis of GF109203X was accomplished in 40% overall yield starting from indole. This work will lead to a short synthesis of mono-N'-alkylated arcyriarubins to accelerate drug discovery.

Keywords: PKC inhibitors, bisindolylmaleimide, GF109203X, arcyriarubin A, protecting group-free synthesis

Introduction

Since the isolation of staurosporine (**1**)[1] in 1977, many indolocarbazoles including rebecamycin (**2**)[2] have been isolated from bacteria, fungi, and invertebrates.[3,4] This family of compounds have attracted much attention because of their wide range of biological activities including inhibition of protein kinase C (PKC).[5] More importantly, a fruitful strategy has been developed to design more selective inhibitors by disrupting the planarity of the indolocarbazole ring system. Among them, bisindolylmaleimides (BIMs)[6,7] derived from arcyriarubin A (**3**)[8,9] are successful examples, which are of interest because of their PKC inhibitory activity. Mono-*N'*-substituted BIMs such as compounds **4-6** (Figure 1: for simplicity, the nitrogen in the maleimide ring is referred to as *N*,

the other two nitrogens in indole rings are marked as *N*' and *N*'' respectively) represent a class of excellent PKC inhibitors.[10]

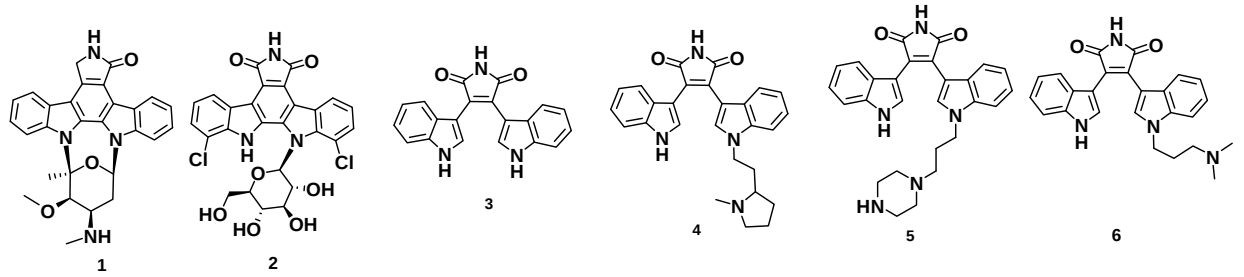
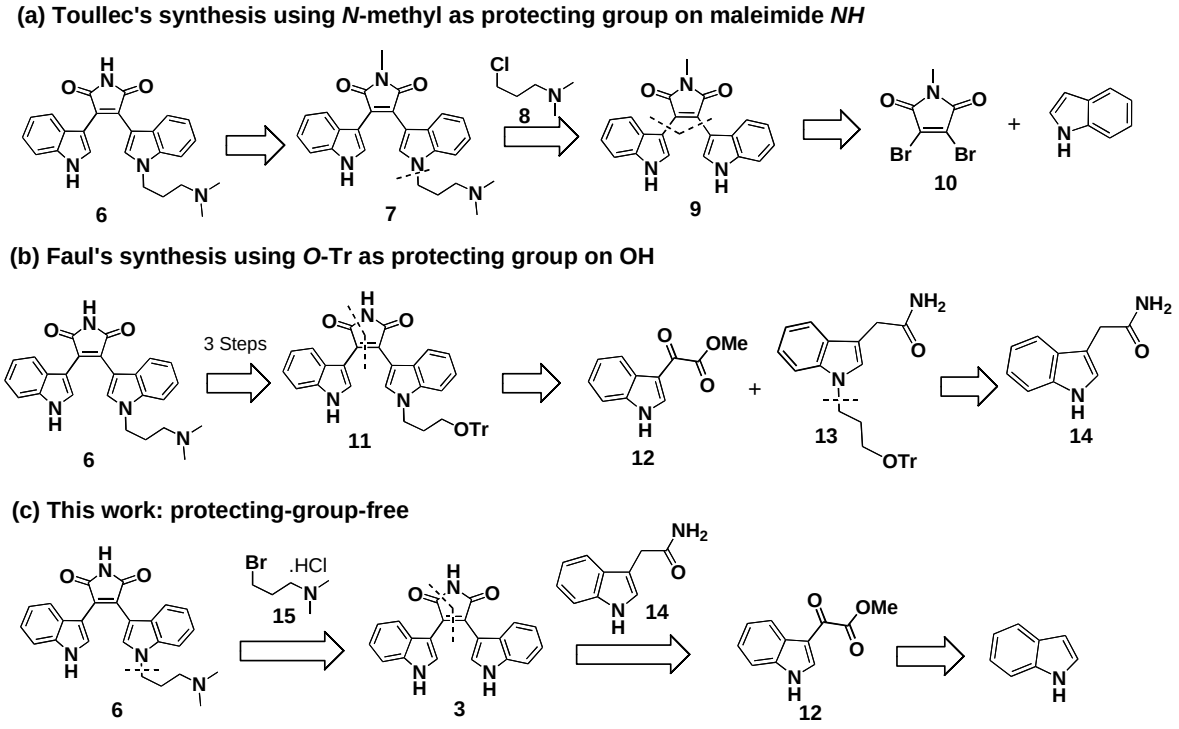


Figure 1. N'-monoalkylated bisindolylmaleimides and related PKC inhibitors.

In particular, GF109203X (**6**) is a highly selective inhibitor to PKCs (IC_{50} = 20 nM，17 nM, 16 nM and 20 nM for PKCα，βI，βII and γ respectively),[11] and it has been widely used in biological studies such as regulation of human platelets,[12] treating Alzheimer's disease,[13] prostate cancer[14] and so on. As a result, GF109203X has attracted attention from the synthetic community.



Scheme 1. Comparison of synthetic strategies. Tr = triphenylmethyl.

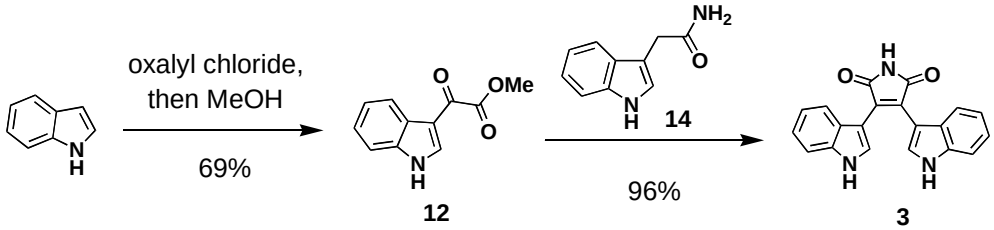
In 1991, the chemical synthesis of GF109203X (**6**) was first reported by Toullec *et al.*[15] in 19% yield starting from indole, using an N-methyl protecting group on the maleimide NH. The bisindolylmaleimide core was built up via addition of indole-derived Grignard reagent to

dibromide **10**,[16,17] and the side-chain was introduced by mono-N'-alkylation of **9** (Scheme 1). Later on, Faul *et al.*[18] developed a more efficient synthesis of GF109203X in 51% yield starting from indole, using an O-trityl (Tr) protecting group (Scheme 1). The binsindolylmaleimide core was made via the coupling[19] between **12** and **13**, and the side-chain was introduced by *N*-alkylation of indole-acetamide **14** at an early stage. Although protecting groups play an important role in organic synthesis,[20] their inclusion in a synthetic route increases the total number of steps by needing protection and deprotection and decreases atom-economy.[21] Thus protecting-group-free synthesis has become a hot research topic in recent years.[22-24]

Considering mono-N'-substituted BIMs such as **4-6** are important lead compounds for PKC inhibitions and further chemical biology studies, we believe it makes sense to develop a general synthesis[25-29] of them all, based on arcyriarubin A with a protecting-group-free strategy, which requires the direct mono-N'-alkylation of arcyriarubin A. In this paper, we report the mono-N'-alkylation of arcyriarubin A and its application to the protecting-group-free synthesis of GF109203X.

Results and Discussion

We commenced our study by making the starting material arcyriarubin A according to Faul's procedure[18, 30] (Scheme 2). Indole reacted with oxalic chloride followed by quenching the reaction with methanol at 0 °C to give methyl indole-3-glyoxylate **12** in 69% yield, which was previously synthesized by using NaOMe in MeOH at – 60 °C.[18] This was reacted with indole-3-acetamide **14** in the presence of *t*-BuOK, the intermediates was converted into arcyriarubin A in 96% yield by acidic aqueous work-up.

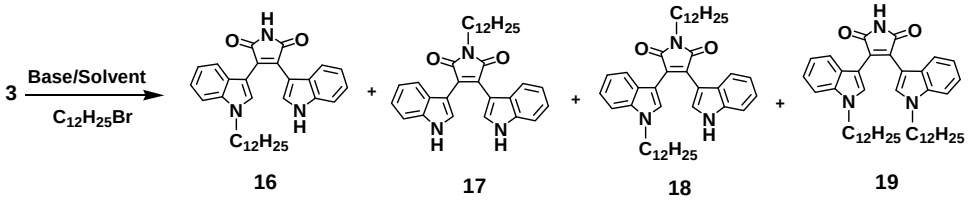


Scheme 2. Two-step synthesis of arcyriarubin A from indole.

Investigation of the reaction of arcyriarubin A (**3**) with *n*-$C_{12}H_{25}Br$ was carried out to see if any mono-N'-substituted product can be obtained. Firstly, we examined the N-alkylation of arcyriarubin A[31,32] in acetone using K_2CO_3 as base (Table 1, entry 1). The red color of arcyriarubin A in acetone turned deeper when it was treated with K_2CO_3, which was reacted with 1.2 eq. of *n*-$C_{12}H_{25}Br$ for seven hours to give mono-N-alkylation product **17** in an isolated yield of 18%. When the reaction was run at 55 °C for 16 hours using three equivalents of K_2CO_3 and three equivlanets of bromide, the mono-*N*-alkylation product (**17**) was isolated in 73% yield, accompanied by the mono-*N'*-alkylated product (**16**) and N,N'-dialkylated product (**18**) in yields

of 7% and 15% respectively. The ^{1}H-NMR spectrum of **16** recorded in $CDCl_3$ showed singlets at 8.65 and 7.86 ppm, which were assigned to the NH of indole and maleimide respectively. Two sets of indole aromatic protons (10 H) could be seen in the range of 8.00-7.00 ppm, which confirmed the asymmetric structure of **16**. Similarly, singlets at 8.56 ppm (2H) and 7.53 ppm (1H) were seen in **17** and **18**, and one set of aromatic protons for **17**, while two sets for **18**. The IR spectra of all the three compounds show weak peak at around 3300 cm^{-1} and a strong absorption at around 1700 cm^{-1}, which are characteristic of NH and C=O. Finally, all three compounds gave satisfactory HR-MS (EI) results (see supplementary materials).

Table 1. N-alkylation of arcyriarubin A (**3**) with n-$C_{12}H_{25}Br$



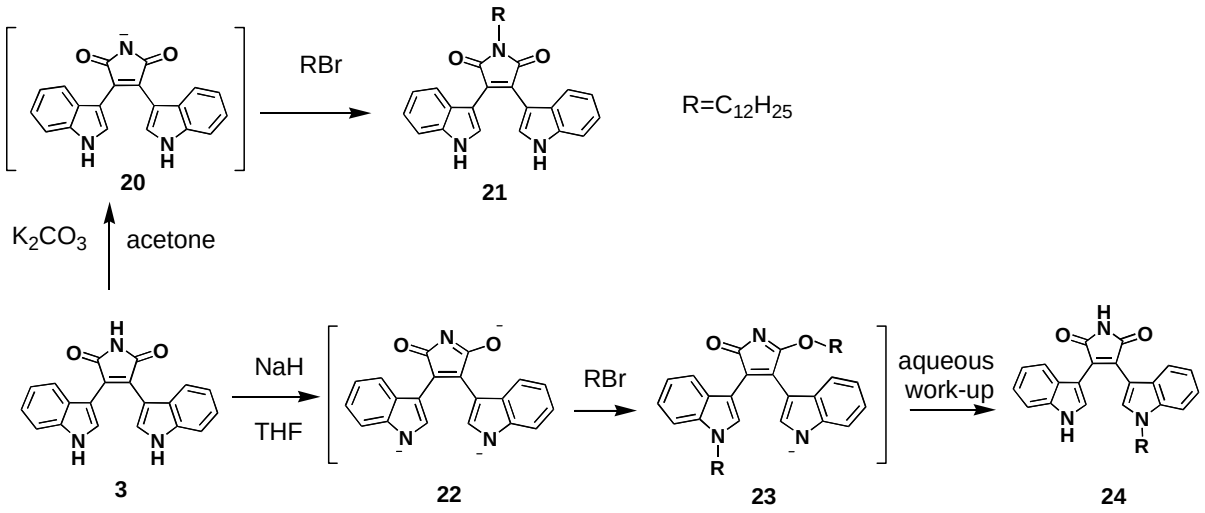
Entry	Base (eq.)	$C_{12}H_{25}Br$ (eq.)	Conditions	Isolated Yield (%)			
				16	**17**	**18**	**19**
1	K_2CO_3(1.2)	1.2	acetone, 25 ^oC, 7 h	NA	18	NA	NA
2	K_2CO_3(3.0)	3.0	acetone, 55 ^oC,16 h	7	73	15	NA
3	LiHMDS (4.0)	2.0	THF, 25 ^oC, 48 h	30(50 [a])	NA	NA	21(35[a])
4	*t*-BuOK (4.0)	2.0	THF, 25 ^oC, 48 h	30(60 [a])	NA	NA	10(20[a])
5	**NaH (4.0)**	**2.0**	**THF, 25 ^oC, 44 h**	**40(70 [a])**	**NA**	**NA**	**15(27[a])**
6	LiHDMS (4.0)	6.0	THF, 55 ^oC, 6 h	30	NA	NA	60
7	*t*-BuOK (4.0)	6.0	THF, 55 ^oC, 6 h	26	NA	NA	62
8	NaH (4.0)	6.0	THF, 55 ^oC, 6 h	NA	NA	NA	91

[a] Yield based on the recovered starting material (BORSM) of **3**.

The mono-N-alkylation of arcyriarubin A other than mono-N'-alkylation resulted as the major product under the aforementioned conditions because the NH of the maleimide unit is more acidic than the NH of indole. Thus we speculated that the use of stronger base would make a difference to the N-alkylation reaction of arcyriarubin A. Indeed, when the reaction was carried out at ambient temperature in THF for 48 hours using LiHMDS, *t*-BuOK or NaH, the color of the reaction mixture turned from red to purple upon the addition of the base to arcyriaribin A. Also, the purple color changed back to red gradually when the reaction mixture was treated with two equivalents of bromododecane. In all cases, the starting material **3** was not fully converted, the mono-N′-alkylated product **16** was isolated as major product, the di-N',N''-alkylated product **19** as minor product, and the mono-N-alkylated products were not isolated (See Table 1, entries 3-5). The isolated yields of mono-N'-alkylated product **16** were 30%, 30% and 40% respectively in the case of LiHMDS, *t*-BuOK and NaH respectively, and 50%, 60% and 70% based on

recovered starting material (BORSM). Besides **16**, the di-N',N''-alkylated product **19** was isolated in a yield of 21%, 10% and 15% correspondingly, and 35%, 20% and 27% BORSM. We also tried the reaction at 55 ^{o}C for four hours using six equivalents of bromododecane, and full conversion of starting material **3** was observed (See Table 1, entry 6-8), the mono-N'-alkylated product **16** was isolated in a yield of 30% and 26% for LiHMDS and *t*-BuOK, and the di-*N*',*N*''-alkylated product **19** a yield of 60% and 62%, respectively. In the case of NaH as base, the di-N',N''-alkylated product **19** was obtained in 91% isolated yield, and the mono-N'-alkylated product **16** was not observed. The characterization of **19** was carried out by ^{1}H-NMR. ^{13}C-NMR, HR-MS, and IR measurements (see supplementary materials). Thus, it is crucial to run the reaction at ambient temperature for a long period using NaH in order to obtain mono-*N*'-alkylated product.

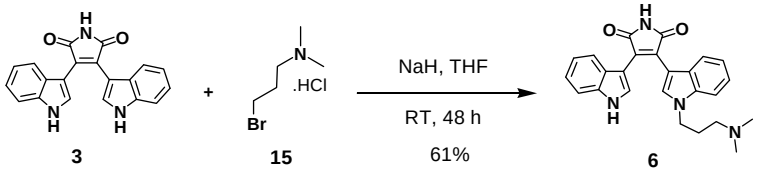
A plausible mechanism for mono-N-substitution and mono-N'-substitution is shown in Scheme **3**. The pK_a of maleimide NH is around 10,[33] hence it can be deprotonated easily in the presence of K_2CO_3 to give the corresponding anion **20**, which reacted with alkyl bromide to give *N*-substituted product **21**. However, the pK_a of an indole NH is about 21,[33] so for deprotonation it requires bases with a pK_a higher than 21. When arcyriarubin A was treated with strong bases such as NaH, all three NHs were completely deprotonated to afford the trianion **22** presumably (Scheme 3),[34,35] which reacted with alkyl bromide to give the N,O-dialkylated product **23**. The conversion of intermediate **23** into final isolated product **24** took place during acidic aqueous work-up. A further study of the mechanism is under investigation.



Scheme 3. Proposed mechanism for the *N*-substitution versus N'-substitution of arcyriarubin A.

Encouraged by the above results, we turned our attention to the synthesis of GF109203X itself (Scheme 2). Some factors were considered in order to obtain optimized conditions: (i) the electrophile **15** is in the form of its HCl salt, which will consume base as well, so that more equivalents of NaH are required; and (ii) lowering the amounts of electrophile **15** will decrease the proportion of di-N',N''-alkylated product. Under the optimized conditions, arcyriarubin A (**3**)

was dissolved in THF and treated with six equivalents of NaH, followed by addition of 1.3 equivalents of bromide **15** in an ice bath. The reaction was continued at ambient temperature for 48 h, standard work-up was followed by flash column chromatography and thereafter crystallization from acetone to give GF109203X (**6**) as a red solid, in an isolated yield of 61%. The starting materials arcyriarubin A was recovered in 23% yield, i.e. 84% yield BORSM. It is worth mentioning that the purification of **6** from starting material **3** by chromatography was quite tricky owing to the presence of the polar dimethylamino group. Fortunately, after careful screening of developing solvents for thin-layer chromatography, we found a special combination of triethylamine and acetone (around 1/12 by volume) to be very helpful for the purification of **6** by flash column chromatography.



Scheme 4. The synthesis of GF109203X via *N'*-substitution of arcyriarubin A.

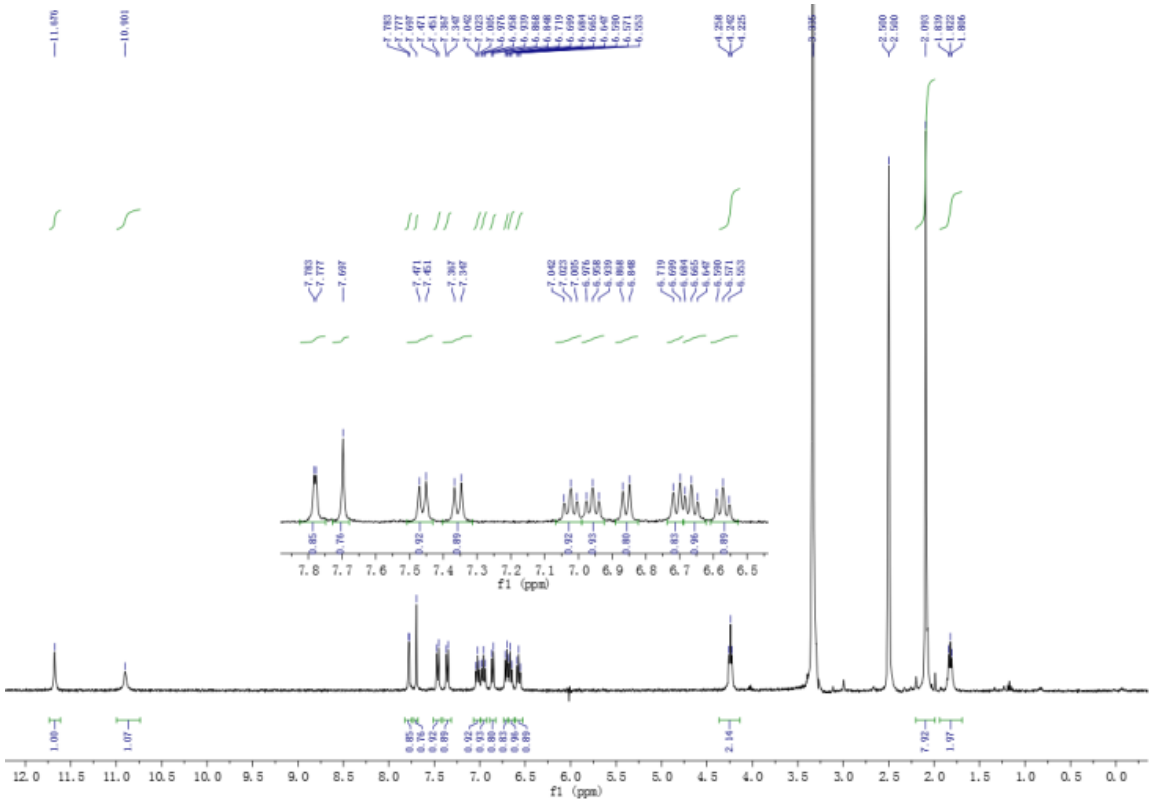


Figure 2. The ^{1}H-NMR spectrum of our synthetic GF109203X (**6**).

The peak at 412.1906 [M^+] in high-resolution mass spectrum revealed the existence of the desired product **6** (reqired 412.1899). The IR data of **6** showed the presence of NH (3396 cm^{-1}) and imide carbonyl (1748, 1703 cm^{-1}).

^{1}H-NMR spectrum of **6** recorded in DMSO-d_6 (Figure **2**) confirmed that **6** had been obtained: two broad singlets at 11.68 ppm (1H) and 10.90 ppm (1H) correspond to NH and N"H, 10 protons in the region of 7.78-5.53 result from two different kinds of indole rings, and the triplets at 4.24 ppm (2H) and 1.82 ppm (2H) as well as a broad singlet at 2.03 ppm (8H) are from the *N*,*N*-dimethyl-3-aminopropanyl side-chain (Figure 2). The ^{1}H-NMR data of our synthetic sample matched well with the ones reported by Toullec[15] and Faul[18] (see supplementary materials).

Conclusions

The mono-N-substitution and mono-N'-substitution of arcyriarubin A (**3**) with bromododecane was accomplished by using K_2CO_3 in acetone and NaH in THF. A plausible mechanism for mono-N-substitution versus mono-N'-substitution of arcyriarubin A was proposed. Based on this result, a protecting-group-free synthesis of GF109203X was achieved in three steps and 40% yield from indole. This work will lead to a general synthesis of mono-N'-alkylated BIMs, and accelerate chemical biological study of this class of important molecules.

Experimental Section

General. All reagents were used as received from commercial sources without further purification or prepared as described in the literature. Tetrahydrofuran was distilled from sodium and benzophenone immediately before use. Reactions were stirred using Teflon-coated magnetic stir bars. Analytical TLC was performed with 0.20 mm silica gel 60F plates. Chromatographic purification of products was carried out by flash chromatography on silica gel (230-400 mesh). Melting points were determined using an electrothermal melting point apparatus or DSC. Infrared spectra were recorded on a Nicolet 8700 Fourier transform spectrometer. NMR spectra were measured in $CDCl_3$ (with TMS as internal standard) or DMSO-d_6 on a Bruker AV400 or Varian INOVA-400M (^{1}H at 400 MHz. ^{13}C at 100 MHz) magnetic resonance spectrometer. Chemical shifts (δ) are reported in ppm, and coupling constants (*J*) are in Hz. The following abbreviations are used to designate the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. High-resolution EI mass spectra (HR-EI-MS) were recorded on an GCT CA127 Micromass UK mass spectrometer.

3-(1-Dodecyl-1*H*-indol-3-yl)-4-(1*H*-indol-3-yl)-1*H*-pyrrole-2,5-dione (16). To a suspension of NaH (60% in oil, 96 mg, 2.40 mmol) in THF (4 mL) was added a solution of **3** (200 mg, 0.60 mmol) in THF (4 mL) at 0 ^{o}C under a nitrogen atmosphere. The resulting mixture was stirred for 30 min and then treated with 1-bromododecane (0.29 mL, 1.20 mmol) slowly. After the reaction

mixture was stirred at 25 °C for 48 h, the reaction was quenched with sat. NH_4Cl (10 mL) at 0 °C, and extracted with EtOAc. The combined organic extracts were washed with water and brine in succession, then dried over anhydrous Na_2SO_4 and concentrated under vacuo. The residue was purified by flash column chromatography (FCC) with EtOAc/petroleum ether =1/4 to afford the title compound as a red solid (115 mg，yield 40%), as well as recovered **3** (60 mg). Rf = 0.33 [EtOAc/petroleum ether = 1/3]. mp 135-137 °C. IR (KBr, cm^{-1}): 3392 (m), 3054 (w), 2925 (s), 2853 (m), 1754 (m), 1698 (s), 1616 (m), 1530 (s), 1461 (m), 1429 (m), 1392 (m), 1341 (m), 1238 (w), 1200 (w), 1126 (w), 740 (m). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.65 (s, 1H), 7.88 (s, 1H), 7.67 (t, *J* 1.2 Hz, 2H), 7.26-7.28 (m, 2H), 7.03-7.23 (m, 2H), 6.92-7.00 (m, 2H), 6.68-6.74 (m, 2H), 4.11 (t, *J* 7.2 Hz, 2H), 1.79 (d, *J* 10.8 Hz, 2H), 1.17-1.28 (m, 18H), 0.83 (t, *J* 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 172.5, 136.3, 135.9, 132.2, 128.9, 128.4, 127.3, 126.3, 125.5, 122.7, 122.3, 122.0, 120.3, 111.3, 109.8, 107.2, 105.6, 47.0, 32.1, 30.1, 29.8, 29.6, 29.5, 29.4, 27.0, 22.8, 14.3. HR-MS (EI): *m/z* 495.2893$[M]^+$ ($C_{32}H_{37}N_3O_2^+$, requires 495.288).

1-Dodecyl-3,4-di(1*H*-indol-3-yl)-1*H*-pyrrole-2,5-dione (17) and 1-dodecyl-3-(1-dodecyl-1*H*-indol-3-yl)-4-(1*H*-indol-3-yl)-1*H*-pyrrole-2,5-dione (18). A solution of **3** (400 mg, 1.20 mmol) in acetone (23 mL) was added to a suspension of K_2CO_3 (500 mg, 3.60 mmol) in acetone (15 mL) under a nitrogen atmosphere, The resulting mixture was stirred for 1 h and then 1-bromododecane (1.04 mL, 3.6 mmol) added. The reaction was heated to 55 °C for another 16 h and then quenched with saturated saline (10 mL), extracted with EtOAc (3 x 10 mL), the extract dried (over Na_2SO_4) and filtered. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography with EtOAc)/petroleum ether = 1/3 as the eluant to afford **16** (42 mg, yield 7%), **17** (432 mg, yield 73%) and **18** (121 mg, yield 15%). Compound **17**: Rf 0.58 EtOAc)/petroleum ether = 1/3. mp 49-51 °C IR (KBr，cm^{-1}): 3393 (m), 2925 (m), 2853 (m), 1754 (w), 1687 (s), 1617 (w), 1530 (m), 1407 (m), 1369 (w), 1240 (w), 1182 (w), 1126 (w), 1101 (w), 1013 (w), 743 (m). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.56 (s, 2H), 7.74 (d, *J* 6.8 Hz, 2H), 7.33 (d, *J* 8.0 Hz, 2H), 7.08 (t, *J* 7.2 Hz, 2H), 6.99 (d, *J* 8.0 Hz, 2H), 6.76 (t, *J* 7.6 Hz, 2H), 3.68 (t, *J* 7.6 Hz, 2H), 1.71 (m, 2H), 1.25-1.35 (m, 18H), 0.87 (t, *J* 4.8 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 172.4, 135.9, 128.4, 127.2, 125.2, 122.4, 120.5, 111.3, 107.4, 38.6, 32.1, 29.8, 29.0, 27.1, 22.8, 14.1. HR-MS (EI): *m/z* 495.2903 $[M]^+$ ($C_{32}H_{37}N_3O_2^+$, requires 495.288). Compound **18**: Rf 0.88 EtOAc/petroleum ether = 1/3; mp 72-74 °C. IR (KBr，cm^{-1}): 3391 (m), 2924 (s), 2853 (s), 1755 (m), 1689 (s), 1615 (m), 1531 (s), 1458 (m), 1437 (m), 1405 (m), 1373 (m), 1239 (m), 1160 (w), 1123 (m), 1102 (w), 1015 (w), 739 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.56 (s, 1H), 7.70-7.72 (br d, 2H), 7.26-7.32 (m, 2H), 7.04-7.10 (m, 2H), 6.98 (t, *J* 6.4 Hz, 2H), 6.73 (t, *J* 7.6 Hz, 2H), 4.12 (t, *J* 7.2 Hz, 2H), 3.68(t, *J* 6.4 Hz, 2H), 1.82 (s, 2H), 1.71(s, 2H), 1.25-1.35(m, 36H), 0.86-0.88 (m, 6H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 172.7, 132.9, 132, 128.7, 128.0, 122.9, 122.6, 122.1, 120.1, 110.2, 109.7, 46.9, 38.5, 32.5, 32.0, 31.1, 30.1, 29.8, 29.5, 29.0, 27.1, 25.0, 22.8, 14.3. HR-MS (EI): *m/z* 663.4772 $[M]^+$ ($C_{44}H_{61}N_3O_2^+$, requires 663.4764).

3,4-bis(1-Dodecyl -1*H*-indol-3-yl)-1*H*-pyrrole-2,5-dione(19). To a suspension of NaH (96 mg, 2.40 mmol) in THF(5mL) was added a solution of **3** (200 mg, 0.60 mmol) in THF (6 mL) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 30 min and then treated with 1-

bromododecane (0.86 mL, 3.60 mmol) slowly. After the reaction mixture was stirred at 55 °C for 6 h, TLC showed the completion of the reaction. The reaction was then quenched with sat. NH_4Cl (10 mL) at 0 °C, extracted with EtOAc. The combined organics were washed with water and brine in succession, then dried over anhydrous Na_2SO_4 and concentrated under vacuo. The residue was purified by flash column chromatography (FCC) with EtOAc/petroleum ether =1/8 to afford a red solid (363 mg，yield 91%). Rf 0.63 EtOAc/petroleum ether = 1/3; mp 90-92 °C (from petroleum ether). IR (KBr, cm^{-1}): 3276 (w), 3049 (w), 2925 (s), 2853 (m), 1759 (m), 1700 (s), 1608 (w), 1531 (m), 1464 (m), 1390 (m), 1389 (m), 1333 (m), 737 (m). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.67 (s, 2H), 7.39 (s,1H), 7.29 (d, *J* 9.0 Hz, 2H), 7.07 (t, *J* 7.5 Hz, 2H) , 6.93 (d, *J* 9.0 Hz, 2H), 6.70 (t, *J* 7.5 Hz, 2H), 4.13 (t, *J* 6.0 Hz, 4H), 1.84 (t, *J* 7.5 Hz, 4H) , 1.28 (br d, 36H), 0.88 (t, *J* 7.5 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) : 172.1, 135.9, 131.5, 127.4, 126.1, 122.1, 121.8, 119.7, 109.3, 105.51, 76.9, 46.6, 31.7, 30.0, 29.8, 29.4, 29.3, 29.2, 29.0, 26.7, 22.5, 13.9. MS: *m/z* 663.4776(EI) ($C_{44}H_{61}N_3O_2^+$, requires 663.4764).

GF109203X (6). To a suspension of NaH (60% in oil, 288 mg, 7.20 mmol) in THF(10 mL) was added a solution of **3** (400 mg, 1.20 mmol) in THF (10 mL) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 30 min and then treated with 3-bromo-*N*,*N*-dimethylpropan-1-amine hydrobromide (385 mg, 1.56 mmol) slowly. After the reaction mixture was stirred at 25 °C for 48 h, the reaction was quenched with sat. NH_4Cl (10 mL) at 0 °C, extracted with EtOAc. The combined organics were washed with water and brine in succession, then dried over anhydrous Na_2SO_4 and concentrated under vacuo. The residue was purified by flash column chromatography (FCC) with acetone)/triethylamine) = 1/12 to afford the title compound as a red solid (300 mg，yield 61%) as well as starting material **3** (92 mg, 23%). Rf 0.61 acetone)/triethylamine = 9/1. IR (KBr, cm^{-1}): 3396 (w), 2943 (w), 1748 (w), 1703 (s), 1610 (w), 1524 (m), 1468 (w), 1445 (w), 1417 (w), 1396 (w), 1340 (w), 1238 (w), 1222 (w), 1006 (w), 742 (m). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.68 (s, 1H), 10.90 (s, 1H), 7.78 (d, *J* 2.4 Hz, 1H), 7.70 (s, 1H), 7.46 (d, *J* 8.0 Hz, 1H), 7.36 (d, *J* 8.8 Hz, 1H), 7.03 (t, *J* 7.6 Hz, 1H), 6.96 (t, *J* 7.6 Hz, 1H), 6.86 (d, *J* 8.0 Hz, 1H), 6.70 (d, *J* 8.0 Hz, 1H), 6.67 (t, *J* 7.6 Hz, 1H), 6.57 (t, *J* 7.6 Hz, 1H), 4.24 (t, *J* 6.4 Hz, 2H), 2.09 (bs, 8H), 1.82 (t, *J* 6.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 173.4, 173.4, 136.5, 136.2, 132.4, 129.7, 128.4, 127.5, 126.5, 125.7, 122.1, 122.1, 121.6, 121.3, 119.9, 119.7, 112.2, 110.6, 105.9, 105.4, 60.2, 56.0, 45.5, 27.9. HR-MS (EI): *m/z* 412.1906 $[M]^+$ ($C_{25}H_{24}N_4O_2^+$, requires 412.1899).

Acknowledgements

We thank Beijing Institute of Technology (Excellent Young Researcher Fund 2012YR0910) and The National Natural Science Foundation of China (No. 21202008) for generous support. Professor Andrea Vasella is thanked for inspiring discussions.

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