Improved Preparation of Sulfur Substituted 3-Vinylpyrrole and Its Application to the Syntheses of Chuangxinmycin Derivatives

Takuji YOSHIDA, Ai ITO, Kei IBUSUKI, Masayuki MURASE,* and Eiichi KOTANI

Showa Pharmaceutical University, Machida, Tokyo 194–8543, Japan. Received March 12, 2001; accepted June 3, 2001

Sulfur substituted 3-vinylpyrrole 10 was prepared from 3-thio-acetylpyrrole 9 by alkylation with alkyl halide in the presence of propylene oxide. Functionalized 4-alkylthioindoles were made by Diels–Alder reaction of the 3-vinylpyrrole 10 with dienophiles. Chuangxinmycin analogues were synthesized by using some of the functionalized 4-alkylthioindoles as key intermediates.

Key words cycloaddition; 3-vinylpyrrole; alkylation; indole; 3-thioacetylpyrrole; propylene oxide

The Diels–Alder (D–A) reaction is one of the most useful reactions in synthetic organic chemistry. Recently, we reported that thiocarbonyl compounds **2**, **4**, and **6** yielded dienes **3**, **5**, and **7**, respectively, through alkylation reactions, and these dienes underwent Diels–Alder reaction with appropriate dienophiles to give functionalized carbazoles, indoles, and benzene derivatives.[1—3] Previously, we found that 4-thioxo-4,5,6,7-tetrahydroindole **8**, having a thioenaminone moiety, gave dehydrochuangxinmycin through alkylation.[4] We also found that the cycloaddition reaction of *N*-methyl-3-vinylpyrrole **5** proceeded smoothly, whereas the NH congener **9** gave no cycloaddition product. This may be due to the lability of vinylpyrrole **10**, and the result was not investigated further.

This paper describes an improved synthesis of sulfur substituted 3-vinylpyrroles **10** and their application to the syntheses of chuangxinmycin having various substituents. In 1978, E. J. Cory *et al.* reported the utility of intramolecular Diels–Alder reaction using propylene oxide as a hydrogen chloride scavenger in the synthesis of gibberellic acid.[5] The application of propylene oxide as a scavenger prompted us to examine its use in the preparation of 3-vinylpyrrole **10** from 3-thioacetylpyrrole **9** and alkyl halide. A preliminary study was done on the reaction of **10a**, generated *in situ* by the reaction of 3-thioacetylpyrrole **9** with methyl iodide in the presence of a large excess of propylene oxide, with dimethyl acetylenedicarboxylate (DMAD) in tetrahydrofuran (THF). The indole **11a** was indeed obtained in 20% overall yield. Similarly, the reactions of **10b** and **10c**, generated *in situ* with benzyl bromide and methyl bromoacetate, with DMAD, gave the indoles **11b** and **11c**, in 17.2 and 27.3% yields respectively. Figure 2 proposes a possible mechanism for the generation of dienes **10**. Reaction of the diene **10c** with *N*-methylmaleimide at 110 °C for 8 h, followed by treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) for 30 min, gave the indole **12a** in 27.3% yield. Similarly, the reaction of the diene **10c** with 3,4-dibromo-*N*-methylmaleimide in THF at room temperature for 8 h, followed by direct *in situ* oxidation, gave **12a** in 36.5% yield.

In general, the cycloaddition reaction of vinylpyrroles **10** with dienophiles were carried out in a fused glass tube at 100 °C under nitrogen for approximately 8 h. The results are summarized in Table 1. The indoles **11c** and **12a** are the key intermediates in the syntheses of substituted chuangxinmycin derivatives.

Synthesis of 7,8-Disubstituted Chuangxinmycin Derivatives Chuangxinmycin **1**, isolated from the microorganism *Actinoplanes tsinanensis* n. sp. of China,[6] is an antibiotic alkaloid bearing a sulfur substituent at the 4-position of the indole nucleus. This compound is known to be active against a variety of Gram-positive and Gram-negative bacteria and is particularly effective in the treatment of *Escherichia coli* infections.[7]

Total synthesis of **1** has already been reported by several groups.[8] We also have reported two routes of formal synthesis.[4,9] Our attention has now been focused on the synthesis of Chuangxinmycin derivatives from the indole **11c**.

Acylation of **11c**, leading to the 3-acetyl derivative **13**, was readily achieved by $SnCl_4$-catalyzed Friedel–Crafts reaction with acetyl chloride (quantitative yield). Compound **13** was then heated in benzene in the presence of ammonium acetate monohydrate and acetic acid for 15 h to give 7,8-disubstituted dehydrochyangxinmycin methyl ester **14** in 65.6% yield.

The ester **14** could not be reduced with Mg–methanol.

We then examined the synthesis of the nor-methyl derivative **17**. Indole **11c** was converted to 3-formyl derivative **15** by the Vilsmeier reaction. Subsequently, without isolating **15**, it was treated with NH_4OAc in AcOH to give the cyclized product **16** in 51.6% yield. Reduction of **16** with Mg–

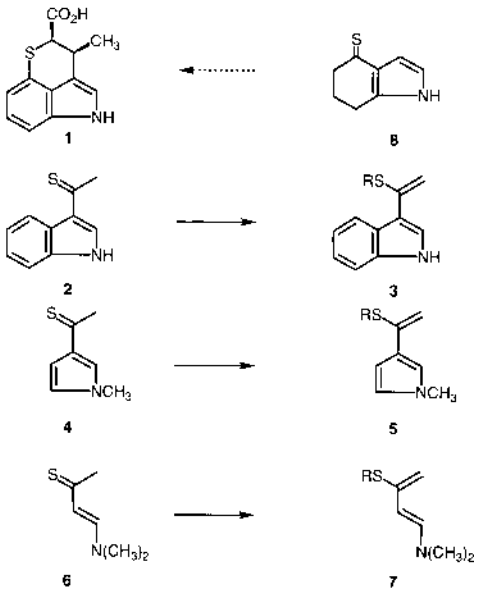

Fig. 1

* To whom correspondence should be addressed. e-mail: murase@ac.shoyaku.ac.jp

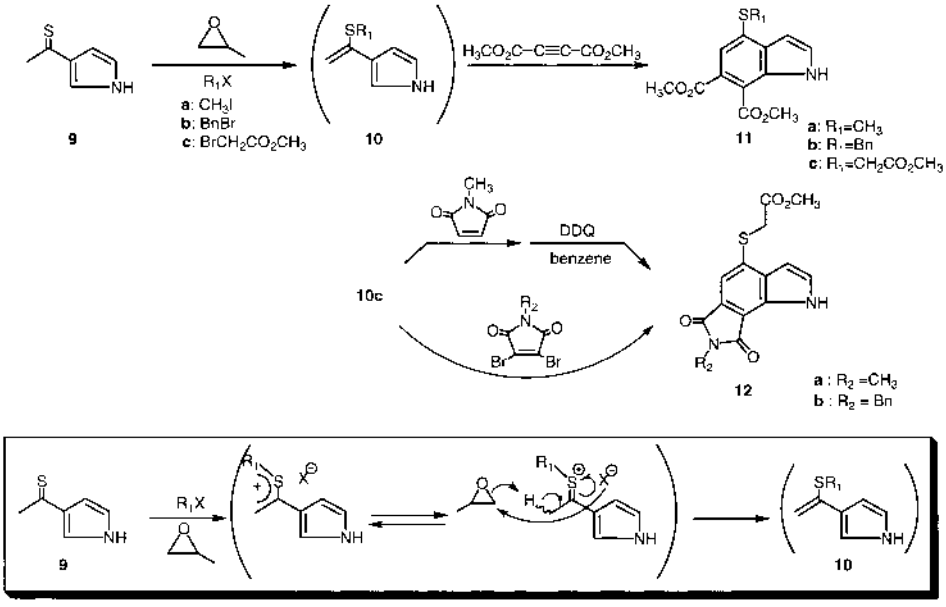

Fig. 2

Table 1. Cycloaddition Reaction of the Diene with Dienophiles

Entry	Diene	Dienophile	Temp. (°C)	Time (h)	Product	Yield (%)[a]
1)	**10a**	$H_3CO_2C-C\equiv C-CO_2CH_3$	110	24	**11a**	20
2)	**10b**	$H_3CO_2C-C\equiv C-CO_2CH_3$	110	24	**11b**	17.2
3)	**10c**	$H_3CO_2C-C\equiv C-CO_2CH_3$	110	8	**11c**	27.3
4)	**10c**		110	8	**12a**[b]	33.8
5)	**10c**		r.t.[c]	8	**12a**	36.5
6)	**10c**		r.t.	8	**12b**	33.7

a) Overall yield from 3-acetylpyrrole. *b*) Obtained by the oxidation of the cycloaddition product without purification. *c*) r.t., room temperature.

methanol gave 7,8-disubstituted nor-methylchuangxinmycin derivative **17** in 49.1% yield (Fig. 3).

Next, the synthesis of nor-methyl derivatives **22** from indoles **12** was examined. Vilsmeier reaction of **12a** with DMF in the presence of $POCl_3$ gave a mixture of **18a** and **19a**. This mixture was refluxed in DMF in the presence of ammonium acetate monohydrate and acetic acid for 6 h to give **19a** in 68% yield. Compound **12b** was allowed to react in a similar manner to give **19b** in 88% yield. The reduction of the double bond of **19b** has been found to be a troublesome problem. The reduction of the C–C double bond on vinyl sulfide tended to accompany rapid desulfurization. Though the hydrogenation of **19b** over palladium/charcoal did not proceed, reduction with $NaBH_4$–$NiCl_2$ led to rapid desulfurization with the formation of 3-substituted-indole **21b**. On the other hand, reduction with Mg–MeOH proceeded with the cleavage of the C ring to furnish thiol **20b**. Treatment of **19b** with LiI in pyridine afforded the hydrolyzed product **22b** in 90.3% yield. Similarly, **19a** gave **22a** in 81.5% yield under the same condition.

We then examined the reduction of the olefinic bond of the unsaturated acid moiety of **22a** and **22b** with Mg–methanol. However, the desired product could not be obtained, probably because of the insolubility of **22a** and **22b**. Thus, **22a** and **22b** were synthesized in 5 steps from 3-acetylpyrrole utilizing propylene oxide. 3-Vinylpyrroles **10** can be prepared readily. Moreover, the Diels–Alder reaction of **10** with dienophiles provides functionalized 4-alkylthioindoles. Studies on the antimicrobial activity of their derivatives are still in progress.

Experimental

All melting points (mp) were determined using a Yanagimoto micromelting point apparatus and are uncorrected. Infrared (IR) spectra were recorded with a JASCO IR-700 spectrometer. ^{1}H- and ^{13}C-NMR spectra were obtained on JNM-GX90, JNM-GX270 and JNM-α500 spectrometers. The chemical shifts are given in ppm (δ), and tetramethylsilane was used as an internal standard ($CDCl_3$, acetone-d_6, DMSO-d_6). Mass spectra were recorded on JEOL JMS-D300, JMS-HX110, and Shimadzu QP-5000 spectrometers. Wako silica gel C-200 (200 mesh), and Fuji Silysia silica gel BW-127 ZH, were used for column chromatography. Thin-layer chromatography (TLC) was done on Merck Kieselgel $60F_{254}$, and spots were detected by ul-

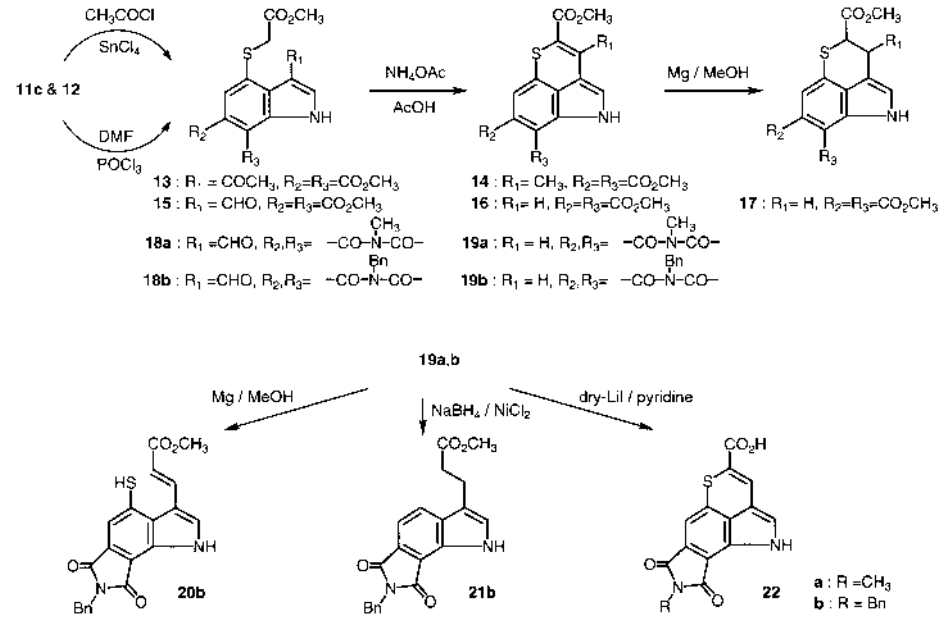

Fig. 3

traviolet (UV) illumination and by spraying 1% $Ce(SO_4)_4$ in 10% H_2SO_4, followed by heating. The organic extract was dried over Na_2SO_4. THF was distilled from sodium/benzophenone under nitrogen before use.

Preparation of the Diene 10 A mixture of **9**, alkyl halide and propylene oxide was heated in a fused glass tube under nitrogen atmosphere under appropriate conditions to give the diene **10**, which was used without purification for the reaction with dienophiles under the condition mentioned in Table 1.

Dimethyl-4-methylthio-1*H*-indole-6,7-dicarboxylate (11a) A mixture of **9** (375 mg, 3 mmol), methyl iodide (1.278 g, 9 mmol), and propylene oxide (2 ml) in dry THF (6 ml) was heated at 55 °C for 4 h in a fused glass tube under nitrogen. The solvent was removed under reduced pressure. A solution of DMAD (511 mg, 3.6 mmol) in dry THF (4 ml) was added to the residue, and the mixture was heated at 110 °C for 24 h in a fused glass tube under nitrogen. The reaction mixture was poured into water and extracted with $CHCl_3$. The organic layer was washed with brine, dried, and evaporated *in vacuo*. The residue was subjected to silica gel column chromatography to yield 167 mg (20%) of **11a** from the chloroform eluate as colorless needles (ether–hexane), mp 120—122 °C. **11a**: ^{1}H-NMR ($CDCl_3$, 270 MHz) δ: 2.62 (3H, s, –SMe), 3.94 (3H, s, CO_2Me), 3.95 (3H, s, CO_2Me), 6.63—6.69 (1H, m, C-3H), 6.99 (1H, s, C-5H), 7.32—7.39 (1H, m, C-2H), 9.80 (1H, br, NH). MS *m/z*: 279 (M^+).

Dimethyl-4-benzylthio-1*H*-indole-6,7-dicarboxylate (11b) A mixture of **9** (375 mg, 3 mmol), benzyl chloride (419.1 mg, 3.3 mmol), and propylene oxide (2 ml) in dry THF (6 ml) was heated at 55 °C for 4 h in a fused glass tube under nitrogen. The solvent was removed under reduced pressure. A solution of DMAD (511 mg, 3.6 mmol) in dry THF (4 ml) was added to the residue, and the mixture was heated at 110 °C for 24 h in a fused glass tube under nitrogen. The reaction mixture was poured into water and extracted with $CHCl_3$. The organic layer was washed with brine, dried, and evaporated *in vacuo*. The residue was subjected to silica gel column chromatography to yield 183 mg (17.2%) of **11b** from the chloroform eluate as colorless needles (ether–hexane), mp 128—129 °C. **11b**: ^{1}H-NMR (acetone-d_6, 270 MHz) δ: 3.85 (3H, s, CO_2Me), 3.92 (3H, s, CO_2Me), 4.42 (2H, s, benzyl H), 6.63—6.69 (1H, m, C-3H), 7.25—7.59 (7H, m, aromatic H), 10.79 (1H, br, NH). MS *m/z*: 355 (M^+). High resolution (HR)-MS Calcd for $C_{19}H_{17}NO_4S$: 355.0877. Found: 355.0857.

Dimethyl-4-methoxycarbonylmethylthio-1*H*-indole-6,7-dicarboxylate (11c) A mixture of **9** (375 mg, 3 mmol), methyl bromoacetate (504.9 mg, 3.3 mmol), and propylene oxide (2 ml) in dry THF (6 ml) was heated at 110 °C for 8 h in a fused glass tube under nitrogen. The solvent was removed under reduced pressure. A solution of DMAD (511 mg, 3.6 mmol) in dry THF (4 ml) was added to the residue, and the mixture was heated at 110 °C for 8 h in a fused glass tube under nitrogen. After the usual work up, the crude product was subjected to silica gel column chromatography to yield 276 mg (27.3%) of **11c** from the chloroform eluate as a brown liquid. **11c**: ^{1}H-NMR ($CDCl_3$) δ: 3.73 (3H, s, CO_2Me), 3.83 (2H, s, –SCH_2), 3.93 (3H, s, CO_2Me), 3.95 (3H, s, CO_2Me), 6.67—6.74 (1H, m, C-3H), 7.22 (1H, s, C-5H), 7.36—7.42 (1H, m, C-2H), 9.79 (1H, br, NH). MS *m/z*: 337 (M^+).

Dimethyl-3-acetyl-4-methoxycarbonylmethylthio-1*H*-indole-6,7-dicarboxylate (13) $SnCl_4$ (78 mg, 0.3 mmol) was slowly added to a solution of **11c** (100 mg, 0.297 mmol) and acetyl chloride (24 mg, 0.3 mmol) in dry benzene (5 ml), with stirring at 0 °C. Stirring was continued for 20 min at ambient temperature. Then, the whole mixture was stirred at room temperature for 2 h more. The reaction mixture was poured into water, then extracted with $CHCl_3$. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, then dried and concentrated.

The addition of ether to the concentrate caused the precipitation of **13**, which was separated through filtration. Recrystallization of the solid from CH_2Cl_2–ether gave a quantitative yield of **13** as colorless needles. mp 182—184 °C. **13**: ^{1}H-NMR ($CDCl_3$) δ: 2.57(3H, s, –Ac), 3.75 (3H, s, CO_2Me), 3.82 (2H, s, –CH_2–), 3.94 (3H, s, CO_2Me), 3.95 (3H, s, CO_2Me), 7.17 (1H, s, C-5H), 7.92 (1H, d, J=3.07 Hz, C-2H), 10.41(1H, br, NH). MS *m/z*: 379 (M^+).

9,10-Dimethoxycarbonyldehydrochuangxinmycin Methyl Ester (14) A mixture of **13** (40 mg, 0.118 mmol), $NH_4OAc \cdot H_2O$ (360 mg, 4.74 mmol), and acetic acid (510 mg, 10.68 mmol) in 3 ml of benzene and 3 ml of THF was heated at 110 °C for 24 h in a fused glass tube. The reaction mixture was cooled, poured into water, and extracted with $CHCl_3$. The extract was dried and evaporated, and the residue was chromatographed on silica gel with $CHCl_3$ as the eluent to yield 25 mg (65.6%) of **14** as yellow crystals. mp 199—201 °C (ether–benzene). **14**: ^{1}H-NMR ($CDCl_3$) δ: 2.44(3H, s, –Me), 3.84 (3H, s, CO_2Me), 3.90 (3H, s, CO_2Me), 3.92 (3H, s, CO_2Me), 6.62 (1H, s, C-8H), 7.16 (1H, d, J=2.14 Hz, C-2H), 9.52(1H, br, NH). MS *m/z*: 361 (M^+). HR-MS Calcd for $C_{17}H_{15}NO_6S$: 361.0620. Found: 361.0633.

Nor-methyl-9,10-dimethoxycarbonyldehydrochuangxinmycin Methyl Ester (16) $POCl_3$ (0.28 ml) was slowly added to dry DMF (0.9 ml) at 0 °C, with stirring under nitrogen. After 10 min, a solution of **11c** (480 mg, 1.4 mmol) in THF (0.5 ml) was added, and the mixture was stirred at 35 °C for 1 h. The reaction mixture was poured into ice-water, 40% aq. NaOH (2 ml) was added, then acidified with 10% HCl to pH 3 and extracted with AcOEt. The extract was dried and evaporated *in vacuo* to give **15**. A solution containing **15**, NH_4OAc (485 mg, 6.3 mmol) and AcOH (756 mg, 12.6 mmol) in DMF (20 ml) was heated at 100 °C for 1 h and then cooled to room temperature. The reaction mixture was poured into ice water and extracted with AcOEt. The organic layer was washed with brine, dried, and evaporated *in vacuo*. The residue was chromatographed over silica gel (AcOEt–hexane, 1 : 3) to give **16** (251 mg, 51.6%) as yellow needles. mp 228.5—229.5 °C. **16**: IR (KBr) cm^{-1}: 1726, 1703. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 3.65 (3H, s, –CO_2CH_3), 3.90 (3H, s, –CO_2CH_3), 3.91 (3H, s, –CO_2CH_3), 6.62 (1H, s, C-8H), 7.10 (1H, d, J=2.2 Hz, C-2H), 7.66 (1H, s, C-4H), 9.50 (1H, br, NH). HR-MS Calcd for $C_{16}H_{13}NO_3S$: 347.0449. Found: 347.0469. MS *m/z*: 347

(M^+).

Nor-methyl-9,10-dimethoxycarbonylchuangxinmycin Methyl Ester (17) Magnesium turning (49 mg, 2.04 mmol) was added to a mixture of **16** (59 mg, 0.17 mmol) and NH_4Cl (445 mg, 10 mmol) in MeOH (1 ml), and the resultant mixture was stirred at room temperature for 3 h. Then, 6 N HCl was added to the reaction mixture and the mixture was extracted with $CHCl_3$. The organic layer was washed with brine, dried, and evaporated *in vacuo*. The residue was chromatographed over silica gel (ether–hexane, 1 : 2) to give **17** (29 mg, 49.1%) as a colorless liquid. **17**: IR (KBr) cm^{-1}: 1725. ^{1}H-NMR ($CDCl_3$, 270 MHz) δ: 3.37 (1H, ddd, J=15.8, 8.5, 1.2 Hz, C-4aH), 3.47 (1H, dd, J=15.8, 4.0 Hz, C-4bH), 3.75 (3H, s, $-CO_2CH_3$), 3.92 (3H, s, $-CO_2CH_3$), 3.95 (3H, s, $-CO_2CH_3$), 4.20 (1H, dd, J=8.5, 4.0 Hz, C-5H), 7.05 (1H, s, C-8H), 7.15 (1H, d, J=1.2 Hz, C-2H), 9.37 (1H, br, NH). MS m/z: 249 (M^+).

7-Methyl-4-methoxycarbonylmethylthiopyrrolo[3,4-*g*]-1*H*-indole-6,8-dione (12a) Method a): A solution of **9** (500 mg, 4 mmol), methyl bromoacetate (734 mg, 4.8 mmol), and propylene oxide (1.22 ml) in dry CH_3CN (10 ml) was heated at 110 °C for 8 h in a fused glass tube under nitrogen. Then, *N*-methylmaleimide (532 mg, 4.8 mmol) was added to the reaction mixture and heated at 110 °C for 8 h in a fused glass tube under nitrogen. The solvent was removed under reduced pressure. The residue was treated with DDQ (908 mg, 4 mmol) and the whole was stirred at room temperature for 30 min, then concentrated. $CHCl_3$ was added to the residue, and insoluble materials were filtered off. The filtrate was evaporated.

The residue was recrystallized from acetone to yield 411 mg (27.3%) of **12a** as yellow needles. Method b): A solution of **9** (250 mg, 2 mmol), methyl bromoacetate (335 mg, 2.2 mmol), and propylene oxide (2 ml) in dry THF (6 ml) was heated at 80 °C for 2 d in a fused glass tube under nitrogen. The solvent was removed under reduced pressure. A solution of 3,4-dibromo-*N*-methylmaleimide (2.9 g, 10.8 mmol) in dry THF (12 ml) was added to the residue and the mixture was stirred at room temperature for 8 h. After the reaction, saturated aqueous $NaHCO_3$ was added, and the reaction mixture was extracted with AcOEt. The organic layer was washed with brine, then dried and concentrated. Acetone was added to the concentrate, the insoluble material was filtered off, and the mother liquor was evaporated to dryness. The residue was recrystallized from acetone to yield 222 mg (36.5%) of **12a** as yellow needles. mp 212.5—214 °C. **12a**: IR (KBr) cm^{-1}: 3284, 1741, 1683. ^{1}H-NMR ($CDCl_3$, 270 MHz) δ: 3.17 (3H, s, N–Me), 3.75 (3H, s, CO_2Me), 3.88 (2H, s, $-CH_2-$), 6.78 (1H, dd, J=3.3, 2.2 Hz, C-3H), 7.47 (1H, dd, J=3.3, 2.2 Hz, C-2H), 7.50 (1H, s, C-5H), 9.42 (1H, br, NH). HR-MS Calcd for $C_{16}H_{12}N_2O_4S$: 304.0516. Found: 304.0516. MS m/z: 304 (M^+).

7-Benzyl-4-methoxycarbonylmethylthiopyrrolo[3,4-*g*]-1*H*-indole-6,8-dione (12b) A mixture of the diene **10c** and 3,4-dibromo-*N*-benzylmaleimide (759 mg, 2.2 mmol) in dry THF (3 ml) was treated as described for **12a** to give **12b** (256 mg, 33.7%) as yellow needles. mp 179—181 °C. **12b**: IR (KBr) cm^{-1}: 1739, 1680, 1429. ^{1}H-NMR (DMSO-d_6, 500 MHz) δ: 3.66 (3H, s, N–Me), 4.23 (2H, s, $-SCH_2-$), 4.78 (2H, s, $-CH_2Ph$), 6.69 (1H, dd, J=3.2, 1.7 Hz, C-3H), 7.25—7.36 (5H, m, aromatic H), 7.40 (1H, s, C-5H), 7.69 (1H, t, J=1.8 Hz, C-2H), 12.88(1H, br, NH). ^{13}C-NMR (DMSO-d_6, 125 MHz) δ: 33.1, 40.6, 52.5, 101.4, 110.1, 112.1, 126.3, 127.6, 131.4, 131.8, 135.0, 137.1, 167.6, 168.7, 169.5. HR-MS Calcd for $C_{20}H_{16}N_2O_4S$: 380.0830. Found: 380.0829. MS m/z: 380 (M^+).

3,4-Dehydro-4-methoxycarbonyl-8-methylpyrrolo[3,4-*g*]thiopyrano-[4,3,2-*cd*]-1*H*-indole-7,9-dione (19a) $POCl_3$ (1.11 ml) was slowly added to dry DMF (3.67 ml) at 0 °C, with stirring under nitrogen. After 10 min, a solution containing **12a** (884 mg, 2.78 mmol) in dry DMF (11.1 ml) was added, and the mixture was stirred at 35 °C for 2 h. The reaction mixture was poured into ice-water, neutralized with 40% aq. NaOH, and the resultant precipitate was collected, washed with water, and dried to give a mixture of **18a** and **19a** (906 mg). A solution of **18a**, **19a**, NH_4OAc (962 mg, 12.5 mmol), and AcOH (1.5 g, 25 mmol) in DMF (16.7 ml) was heated to reflux for 6 h and then cooled to room temperature. The reaction mixture was poured into ice-water and the resultant precipitate was collected, washed with water, dried, and recrystallized from THF to give 602 mg (69%) of **19a** as deep green needles. mp >300 °C. **19a**: IR (KBr) cm^{-1}: 1750, 1709, 1693. ^{1}H-NMR (acetone-d_6, 500 MHz) δ: 3.11 (3H, s, N–Me), 3.86 (3H, s, $-CO_2CH_3$), 6.98 (1H, s, C-6H), 7.17 (1H, d, J=2.4 Hz, C-2H), 7.62 (1H, s, C-3H), 10.58 (1H, br, NH). HR-MS Calcd for $C_{15}H_{10}N_2O_4S$: 314.0361. Found: 314.0369. MS m/z: 314 (M^+).

3,4-Dehydro-8-benzyl-4-methoxycarbonylpyrrolo[3,4-*g*]thiopyrano-[4,3,2-*cd*]-1*H*-indole-7,9-dione (19b) $POCl_3$ (2.6 ml) was slowly added to dry DMF (8.6 ml) at 0 °C, with stirring under nitrogen.

After 10 min, a solution of **12b** (825 mg, 2.17 mmol) in dry DMF (8.7 ml) was added, and the mixture was stirred at 35 °C for 6 h. The reaction mixture was poured into ice-water, neutralized with 40% aq. NaOH, and the resultant precipitate was collected, washed with water, and dried to give a mixture of **18b** and **19b** (906 mg). A solution of **18b**, **19b**, NH_4OAc (751 mg, 9.77 mmol) and AcOH (1.17 g, 19.53 mmol) in DMF (13 ml) was heated to reflux for 5 h and then cooled to room temperature. The reaction mixture was poured into ice-water and extracted with AcOEt. The organic layer was washed with brine, dried, and concentrated *in vacuo*. The residue was recrystallized from acetone to give **19b** (746 mg, 88.2%) as dark reddish brown needles. mp 266—268 °C. **19b**: IR (KBr) cm^{-1}: 1740, 1692, 1576. ^{1}H-NMR (DMSO-d_6, 500 MHz) δ: 3.77 (3H, s, $-CO_2CH_3$), 4.70 (2H, s, $-CH_2-$), 6.94 (1H, s, C-6H), 7.25—7.35 (5H, m, aromatic H), 7.43 (1H, d, J=2.4 Hz, C-2H), 7.59 (1H, s, C-3H), 12.28 (1H, br, NH). ^{13}C-NMR (DMSO-d_6, 125 MHz) δ: 40.4, 52.6, 107.0, 111.1, 113.1, 120.7, 125.9, 126.9, 127.1, 127.2, 127.9, 128.5, 130.4, 130.5, 136.9, 163.0, 166.8, 168.0. HR-MS Calcd for $C_{21}H_{14}N_2O_4S$: 390.0674. Found: 390.0679. MS m/z: 390 (M^+).

7-Benzyl-3-methoxycarbonylvinyl-4-mercaptopyrrolo[3,4-*g*]-1*H*-indole-6,8-dione (20b) Magnesium turning (486 mg, 20 mmol) was added to a mixture of **19b** (195 mg, 0.5 mmol) and NH_4Cl (445 mg, 10 mmol), in dry THF (29 ml) and MeOH (24 ml), and the resultant mixture was stirred at room temperature for 30 min. A saturated NH_4Cl solution was added to the reaction mixture and the mixture was extracted with AcOEt. The organic layer was washed with brine, dried, and evaporated *in vacuo*. The residue was recrystallized from THF to give **20b** (126 mg, 64.3%) as yellow needles. mp 226—228 °C. **20b**: IR (KBr) cm^{-1}: 1665, 1439, 1261. ^{1}H-NMR (DMSO-d_6, 270 MHz) δ: 3.38 (3H, s, Me), 4.59 (2H, ABq, J=15.57, 15.57 Hz, $-CH_2-$), 5.54 (1H, d, J=8.9 Hz, olefinic H), 6.65 (1H, d, J=8.9 Hz olefinic H), 6.74 (1H, s, C-5H), 7.22—7.37 (5H, m, aromatic H), 7.65 (1H, s, C-2H), 11.97 (1H, br, NH). ^{13}C-NMR (DMSO-d_6, 125 MHz) δ: 41.8, 52.5, 80.6, 107.7, 112.2, 112.5, 120.0, 123.7, 126.9, 127.4, 127.9, 128.4×2, 133.1, 137.9, 144.8, 163.3, 165.5. HR-MS Calcd for $C_{21}H_{16}N_2O_4S$: 392.0831. Found: 392.0845. MS m/z: 392 (M^+).

7-Benzyl-3-methoxycarbonylethylpyrrolo[3,4-*g*]-1*H*-indole-6,8-dione (21b) $NiCl_2\cdot 6H_2O$ (35.7 mg, 0.15 mmol) and $NaBH_4$ (56.7 mg, 1.5 mmol) were added to a solution of **19b** (39 mg, 1 mmol) in MeOH (70 ml) at 0 °C, and the mixture was stirred at the same temperature for 5 min. Saturated NH_4Cl solution was added to the reaction mixture and the mixture was extracted with AcOEt. The organic layer was washed with brine, dried, and evaporated *in vacuo*. The residue was chromatographed over silica gel (AcOEt–hexane, 1 : 3) to give **21b** (30.1 mg, 83.1%) as yellow needles. mp 153—155 °C. **21b**: IR (KBr) cm^{-1}: 1760, 1736, 1695. ^{1}H-NMR ($CDCl_3$, 90 MHz) δ: 2.70 (2H, t, J=4.7 Hz, $-CH_2-$), 3.11 (2H, t, J=4.7 Hz, $-CH_2-$), 3.66 (3H, s, Me), 4.84 (2H, s, benzyl H), 7.24—7.45 (6H, m, aromatic H and C-2H), 7.56 (1H, d, J=7.9 Hz, C-4H), 7.85 (1H, d, J=7.9 Hz, C-5H), 9.02 (1H, br, NH). HR-MS Calcd for $C_{21}H_{18}N_2O_4$: 362.1266. Found: 362.1295. MS m/z: 362 (M^+).

4-Carboxy-3,4-dehydro-8-methylpyrrolo[3,4-*g*]thiopyrano[4,3,2-*cd*]-1*H*-indole-7,9-dione (22a) Dry-LiI (540 mg, 3.6 mmol) was added to a solution of **19a** (56.4 mg, 0.18 mmol) in dry pyridine (15 ml), and the mixture was heated under reflux for 8 h. The reaction mixture was poured into ice-water, its pH adjusted to 1, and it was then extracted with AcOEt. The organic layer was washed with brine, then dried and evaporated. The residue was recrystallized from THF to give **22a** (44 mg, 81.5%) as dark reddish brown needles. mp >300 °C. **22a**: IR (KBr) cm^{-1}: 1754, 1690, 1574. ^{1}H-NMR (DMSO-d_6, 270 MHz) δ: 2.97 (3H, s, Me), 6.91 (1H, s, C-6H), 7.04—7.42 (1H, m, C-2H), 7.55 (1H, s, C-3H). ^{13}C-NMR (DMSO-d_6, 125 MHz) δ: 23.3, 106.6, 111.3, 113.3, 122.4, 125.1, 126.8, 127.0, 130.3, 130.7, 136.5, 164.2, 167.2, 168.4. HR-MS Calcd for $C_{14}H_8N_2O_4S_1$: 300.0204. Found: 300.0178. MS m/z: 300 (M^+).

4-Carboxy-3,4-dehydro-8-benzylpyrrolo[3,4-*g*]thiopyrano[4,3,2-*cd*]-1*H*-indole-7,9-dione (22b) Dry-LiI (883 mg, 6.6 mmol) was added to a solution of **19b** (130 mg, 0.33 mmol) in dry pyridine (15 ml), and the mixture was heated under reflux for 8 h. The reaction mixture was poured into ice-water, its pH adjusted to 1, and it was then extracted with AcOEt. The organic layer was washed with brine, then dried and evaporated. The residue was recrystallized from THF to give **22b** (112 mg, 90.3%) as dark reddish brown needles. mp >300 °C. **22b**: IR (KBr) cm^{-1}: 1755, 1680, 1572. ^{1}H-NMR (DMSO-d_6, 500 MHz) δ: 4.71 (2H, s, $-CH_2-$), 6.97 (1H, s, C-6H), 7.25—7.35 (5H, m, aromatic H), 7.44 (1H, d, J=2.4 Hz, C-2H), 7.57 (1H, s, C-3H), 12.25 (1H, br, NH). ^{13}C-NMR (DMSO-d_6, 125 MHz) δ: 40.5, 107.0, 111.1, 113.5, 122.9, 125.3, 126.9, 127.0, 127.2, 127.3, 128.6, 130.6, 130.7, 137.0, 137.3, 164.3, 166.9, 168.2. HR-MS Calcd for $C_{20}H_{12}O_4N_2S_1$: 376.0517. Found: 376.0519. MS m/z: 376 (M^+).

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