Further study on the transformation of β-(1-hydroxybut-3-enyl)-indoles into 1-β-(indolyl)buta-1,3-diene, yuehchukene, murrapanine and analogues

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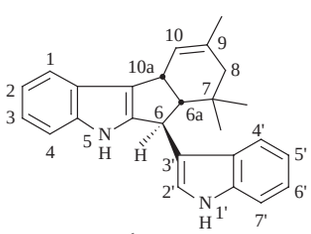
β-(1-Hydroxybut-3-enyl)indoles have been converted into three indole natural products: yuehchukene 1, β-(dehydroprenyl)indole 2, murrapanine 3 and other analogues in a one step procedure under various acid-catalysed reaction conditions in THF. A one-pot synthesis of bisnoryuehchukene 15 starting from indole-3-carboxaldehyde was also achieved using a similar approach. β-(1-Hydroxybut-3-enyl)indoles are presumed to be dehydrated to 1-(β-indolyl)buta-1,3-dienes which then react further to give yuehchukene, murrapanine and other derivatives *via* a Diels–Alder pathway. The yields of 3 and normurrapanine 31 could be improved by using an aerial oxidation method. Murrapanine and analogues were found to exhibit potent cytotoxicity towards various cancer cell lines.

Introduction

Yuehchukene **1**, an indole natural product, was isolated initially from the roots of *Murraya paniculata* (L.) Jack[1] and later from other *Murraya* species[2a,b] in racemic form. Compound **1** has been shown to be a dimeric product of β-(dehydroprenyl)indole **2**. Diene **2** was isolated later from the stem and root barks of *Murrilia caloxylon* (R.) Swingle.[2c] A cytotoxic indole natural product, murrapanine **3**, which is also derived from **2**, has been obtained from the root barks of *Murraya paniculata var. omphalocarpa*.[3] Yuehchukene has been shown to exhibit anti-implantation activity in rats,[4] mice[5] and moderate activity in guinea pigs[6] and is considered to be a potential fertility regulating agent. Due to the interesting biological activity and the paucity of this compound from natural sources, yuehchukene has been a synthetic target of several research groups.[7] A number of yuehchukene analogues also have been prepared.[7b,d,e,g,8]



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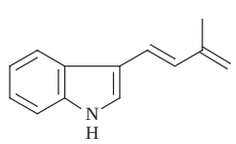

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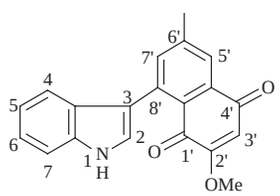

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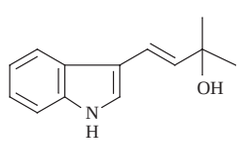

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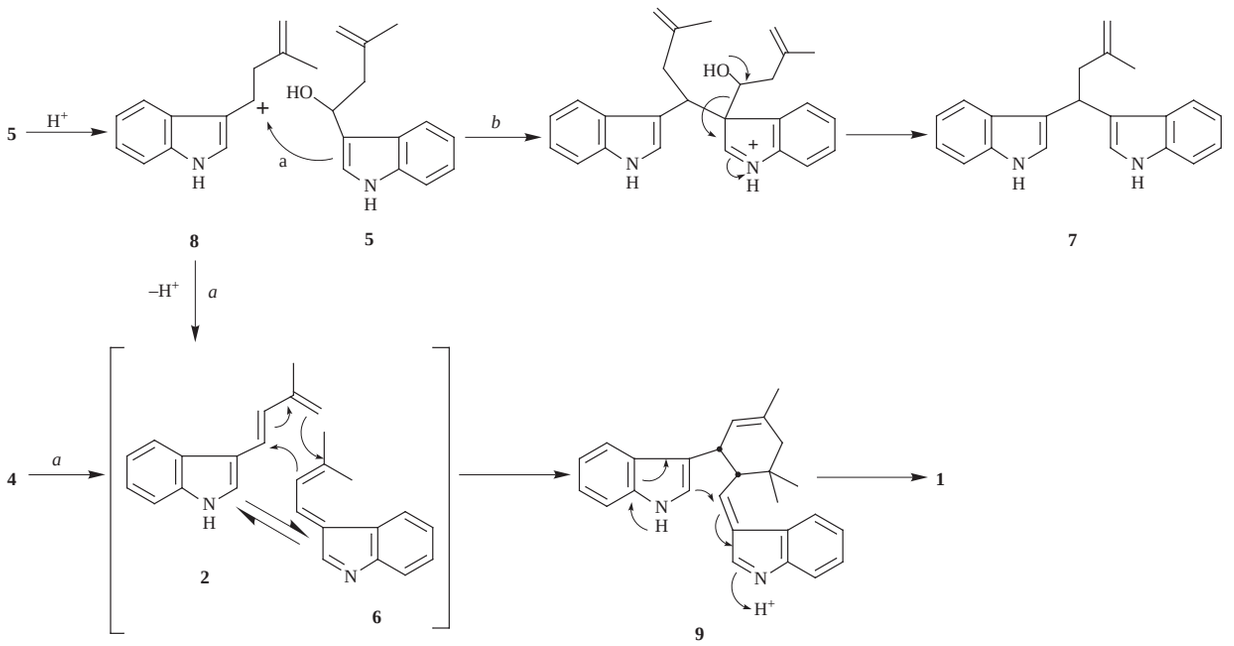
A previous study showed that acid-catalysed dimerization of diene **2**[7a] could provide yuehchukene rapidly, although not in satisfactory yield. We also have reported that (*E*)-β-(3-hydroxy-3-methylbutenyl)indole **4** could be directly converted into **1** *via* **2** in better yield by an acid-catalysed reaction in benzene.[7f,i] Further study showed that the above reaction condition could not convert β-(1-hydroxy-3-methylbut-3-enyl)indole **5** into **1**, however, heating **5** in a neutral solution of ethylene glycol and water could afford **1**.[7i] Both alcohols were supposed to undergo dehydration to diene **2** and dienophile **6**, which interact further *via* a Diels–Alder cyclisation to give yuehchukene (Scheme 1). Our previous study[7i] revealed that **5**, which was converted easily into bis-indole **7**, but not into **1**, in an acidic solution of benzene or dichloromethane, could be transformed into yuehchukene in an acidic solution of ethylene glycol. Both pathways are shown in Scheme 1. It was considered that the solvation by ethylene glycol of cation **8** might deter nucleophilic attack by molecules of **5** on **8**, making the transformation of **5** into diene **2** and the further dimerized product **1** more favorable. Our further study showed that the reaction of **5** with acid in THF could yield diene **2** efficiently, implying that further reaction of **2** with suitable dienophiles could lead to the formation of Diels–Alder products *in situ*. This report describes the full details of our efforts to develop a general and efficient method for the synthesis of indole natural products **1**–**3**, and their analogues from easily available β-(1-hydroxybut-3-enyl)indoles[9] by using this approach. Cytotoxicity of murrapanine and analogues towards various cancer cell lines is also reported herein.

Results and discussion

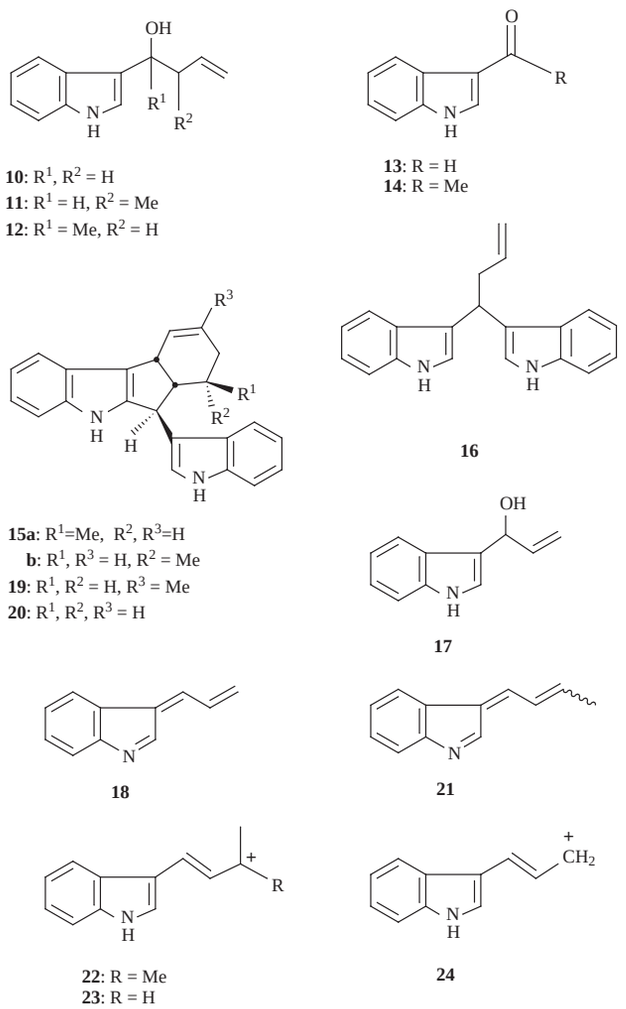
By using the method developed by us for the preparation of alcohol **5**[7i] and β-(1-hydroxybut-3-enyl)indole **10**,[8h] β-(1-hydroxy-2-methylbut-3-enyl)indole **11** could be prepared from the reaction of indole-3-carboxaldehyde **13** with crotylmagnesium bromide in 97% yield. β-(1-Hydroxy-1-methylbut-3-enyl)indole **12** also was synthesized in 95% yield from the reaction of allylmagnesium chloride with 3-acetylindole **14**. Studies on the acid-catalysed reaction of β-(1-hydroxybut-3-enyl)indoles in THF were then carried out.

Yuehchukene and analogues

The new acid-catalysed reaction of alcohols **5** and **10** was investigated in order to convert these two compounds into dienes and yuehchukene analogues in a one-step transformation. We found that treatment of **5** with a catalytic amount of TFA in THF at room temperature could convert **5** slowly to diene **2**, but not to bis-indole **7**. Thus, it was assumed that acid-catalysed reaction of alcohols **5** and **10** in THF could lead to the formation of yuehchukene and bisnoryuehchukene *via*



Scheme 1



pathway *a* of Scheme 1. Further investigation showed that treatment of both **5** and **10** with TFA in refluxing THF under nitrogen for 20–24 h could afford both yuehchukene **1** and bisnoryuehchukene **15a** and **15b** (4 : 1) in 28% and 46% yields, respectively. Both bis-indoles, **7** and **16**, could be isolated only in trace quantities (<1%) in the above reaction conditions. In a related reaction, treatment of alcohol **4** with TFA under the above reaction conditions was also found to furnish **1** in similar yield (26%). In view of the fact that β-(1-hydroxypropenyl)indole **17**[8h] could be a useful synthon of dienophile **18**, the reactions of **17** with both alcohols **5** and **10** were studied. Slow addition of **17** (1.5 equiv.) into a refluxing THF solution of **5** and a catalytic amount of TFA over a period of 1 h gave bisnoryuehchukene **19** in 18% yield. Also, trinoryuehchukene **20** could be afforded in 17% yield by reaction of **17** with **10** under similar reaction conditions. Although the yields of the above two reactions are low, neither **1** nor **20** could be isolated from the former or from the latter reactions. Thus, these results might be used to support the assumption that reactions of this type do indeed proceed *via* a Diels–Alder pathway, rather than a cationic stepwise cyclisation process[7a] since **18** is the better dienophile in comparison with its homologues **6** and **21** from the point of view of any steric effects in Diels–Alder reactions. If the reactions proceed *via* the cationic stepwise cyclisation pathway, both **1** and **15** should be obtained since cations **22** and **23** are more stable and would be formed more easily than **24**.

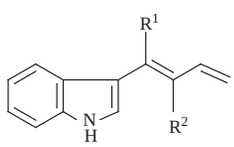
Although yuehchukene **1** and analogues **15**, **19** and **20** could be synthesised efficiently *via* the synthetic routes described above, the yields of the above products are not satisfactory. Wenkert has suggested previously that Diels–Alder reaction of diene **2** and its tautomer **6** could not only give the *endo* intermediate **9** but also the *exo* intermediate with an approximate ratio of 1 : 1.[7b] Since the *exo* intermediate might undergo polymerization immediately upon its formation, he postulated that a reaction of this type could only give yuehchukene or one of its analogues in 50% yield at best. Our previous work and present investigation also showed that 6a-*epi*-yuehchukene could not be isolated *via* the Diels–Alder reaction of 1-β-(indolyl)buta-1,3-dienes and the corresponding dienophiles. Thus, our results are consistent with Wenkert's prediction.

The above results indicate that in acidic THF β-(1-hydroxybut-3-enyl)indoles could be dehydrated efficiently to dienes which could be further converted into yuehchukene and analogues *in situ*. Reactions of both dienes **2** and **25** with alcohol **17** under the above reaction conditions have also been investigated. It was found that the corresponding yuehchukene analogues **19** and **20** could be obtained from the above two reactions, but in yields only similar to those from the direct reaction of both alcohols **5** and **10** with **17**. The one-pot syntheses for both **1** and **15** from **13** were investigated too. Follow-

ing reaction of **13** with isobutenylmagnesium chloride in THF, conc. aqueous HCl was slowly introduced into the above mixture until the solution was acidified. The acidic mixture was further reacted under reflux for 2 h to afford an intractable mixture of **1** and other unknown compounds. In spite of the failure of the above one-pot synthesis in obtaining pure yuehchukene **1**, an attempted one-pot synthesis of **15** was carried out. Surprisingly, starting from the reaction of **13** with allylmagnesium chloride, followed by acidification and further thermal reaction, compound **15** could be cleanly obtained in 48% yield from **13** by using the above procedure. Obviously, this one-pot synthesis provides bisnoryuehchukene **15** in much better yield than those reported previously.[7b,8h]

1-(β-Indolyl)buta-1,3-dienes

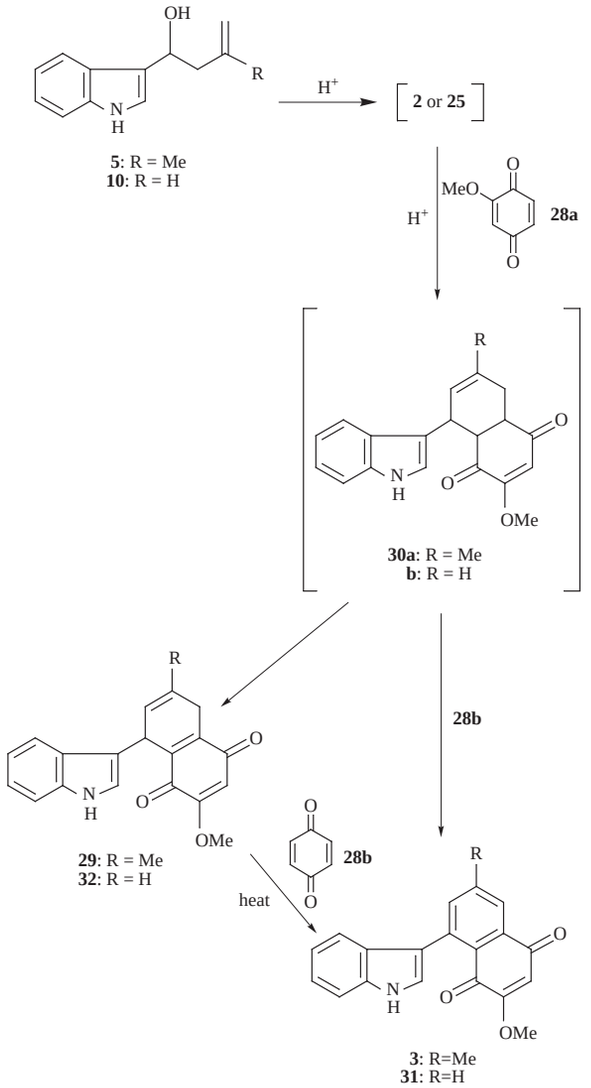
Early approaches to diene **2**[3,7a,7b,10] proved to be unsatisfactory from the point of view of lengthy synthetic schemes and poor overall yields. Our study revealed that reaction of alcohol **4** with a catalytic amount of TFA in THF at 50–55 °C for 2 h could afford diene **2** in 58–65% yield. By using the above reaction conditions, alcohol **10** was dehydrated to 1-(β-indolyl)buta-1,3-diene **25**[7b] in 67–72% yield. Further study showed that the yield of **25** could be raised to 95% if the crude product was purified rapidly by using a short silica gel column. Although previous reports showed that diene **2** could be converted into **1** in benzene by reaction with acid at 50–60 °C,[7a] it seems that these two dienes are more stable in THF as they could not be transformed into the corresponding dimers **1** and **15** by TFA at a similar temperature. If the reactions were carried out under reflux, the dimerization of dienes was gradually detected. By using the above method, both alcohols **11** and **12** were also converted into the corresponding dienes **26**[11] (*E*/*Z* = 2.5 : 1) and **27** in 73% and 75% yields, respectively. However, it was found that both dienes **26** and **27** could not be transformed into the corresponding dimers, even in refluxing THF, under the above reaction conditions.



25: R^1, R^2 = H
26: R^1 = H, R^2 = Me
27: R^1 = Me, R^2 = H

Murrapanine and analogues

In order to demonstrate the potential of this carbon–carbon bond-forming reaction we applied the above method to a total synthesis of murrapanine **3**, as it was assumed that diene **2**, formed by the dehydration of **5**, could undergo Diels–Alder reaction with methoxyquinone **28a** *in situ*. Reaction of alcohol **5** with a catalytic amount of TFA and methoxyquinone **28a** (3.5 equiv.) in THF at room temperature for 4 days yielded **3** (16%) and dihydromurrapanine **29** (20%). Reaction of diene **2** with **28a** under the same conditions gave similar results. The conversion of **29** into **3** is very slow, even in the presence of *p*-benzoquinone **28b**. Introducing *p*-benzoquinone (2.0 equiv.) into the reacting mixture of **28a** and **5** in THF after the reaction has proceeded for 12 h, and continuing the reaction for another 60 h at 25 °C leads to the isolation of **3** in 20% and **29** in 15% yields. If the reaction proceeded under reflux for 3 days after the addition of *p*-benzoquinone, both **3** and **29** were isolated in 30% and 24% yields, respectively. The high overall yield of **3** and **29** in the last reaction may arise from the dehydrogenation of the unreacted intermediate **30**, which could not be purified from the former two reactions, by *p*-benzoquinone under reflux in THF. The pathway for this reaction could be formulated as shown in Scheme 2.



Scheme 2

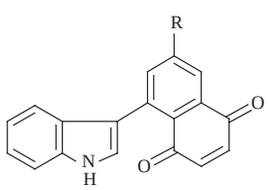
In order to improve the yield of **3**, we have to investigate a useful method which could convert **29** into **3** efficiently. It was found that reaction of **29** with DDQ, a strong dehydrogenation reagent,[12] could not afford **3**. Instead, it gave only an intractable mixture. We finally discovered that **29** could be converted into **3** smoothly by aerial oxidation in silica gel by monitoring the reaction mixture on TLC plates. Based on the above, the following procedure was developed in an attempt to find a method which could convert **29** into **3** more efficiently. Following the reaction of **5** with **28a** in acidic THF, *p*-benzoquinone **28b** (2 equiv.) was introduced and the reaction was continued for another 24 h. The above mixture was mixed with silica gel and was evaporated to remove THF. The mixture, absorbed onto silica gel, was exposed to the air for 4 days and was found to afford murrapanine **3** (56%) together with a trace amount of **29** (<1%). Similarly, the aerial oxidation of the reaction mixture of alcohol **10** and **28a** on silica gel in the presence of **28b**, afforded normurrapanine **31** in 31% yield. Dihydronormurrapanine **32** was not isolated from the above reaction. In the absence of silica gel, the reaction of **28b** with the reacting mixture of **10** and **28a** afforded **31** in only 20% yield, and its dihydro derivative **32** in 10% yield. Although murrapanine **3** and normurrapanine **31** have previously been synthesized,[3,8h] our present study provides both compounds in better yields. The above method also has been used in the synthesis of demethoxymurrapanines **33a**,**b**, however the yields for the above two compounds were found to be unsatisfactory (6–10%). In order to raise the yields of compounds **33a**,**b**, the thermally-induced

Table 1 Cytotoxicity[a] of murrapanines

Compound	cell lines ED_{50} (μg cm^{-3}) P-388	KB	HT-29	A-549
3	0.6	2.8[8h]	0.9	1.5
31	0.08	0.9[8h]	0.4	0.7
33a	0.03	0.3	0.05	0.1
33b	0.01	0.3	0.2	0.4
mithramycin[b]	0.06	0.08	0.08	0.07

[a] For significant activity of pure compounds an ED_{50} value of ⩽4.0 μg cm^{-3} is required.[13] [b] Mithramycin was used as a positive control.

reactions of alcohols **5** and **10** with *p*-benzoquinone **28b** in a neutral solution of ethylene glycol and water were carried out at 155 °C for 1 h and afforded **33a** and **33b** in 26% and 27% yields, respectively. Although murrapanine and its analogues could be prepared easily in the above one-step transformations, a substantial amount of intractable mixtures were also obtained as red gummy materials in these reactions, rendering decreased yields of the desired compounds. Compounds **3** and **31** have been found to exhibit significant cytotoxicity to KB (human nasopharyngeal carcinoma) cells with ED_{50}'s of 2.8 and 0.9 μg cm^{-3}, respectively.[8h] Demethoxy analogues **33a** and **33b** were found to exhibit stronger cytotoxicity against the growth of KB cells, with ED_{50}'s of 0.3 μg cm^{-3} for both compounds. Compounds **3**, **31**, **33a** and **33b** were also shown to exhibit potent cytotoxicity toward P-388 (murine lymphocytic leukaemia), A-549 (human lung adenocarcinoma) and HT-29 (human colon adenocarcinoma) cancer cells (Table 1). All of these results indicate that the demethoxymurrapanines (**33a**,**b**) are more active against the growth of the tested cancer cell lines in comparison with the methoxynapthoquinones **3** and **31**.



33a: R = Me
b: R = H

In summary, our study on acid-catalysed reaction of β-(1-hydroxybut-3-enyl)indoles provides useful synthetic routes to 1-(β-indolyl)buta-1,3-dienes, and their derived products; yuehchukene, murrapanine and their analogues. These were formed in a one-step transformation in acceptable overall yields *via* generation of 1-(β-indolyl)buta-1,3-dienes and then further Diels–Alder reaction with the relevant dienophiles *in situ*. Although demethoxymurrapanines **33a**,**b** could not be synthesized in good yields by the above acid-catalysed method, thermally-induced reactions of alcohols **5** and **10** with *p*-benzoquinone did afford **33a** and **33b** in acceptable yields. Murrapanine and its analogues prepared by us all showed significant cytotoxicity towards various cancer cells. Demethoxymurrapanines **33a**,**b** were found to be more active against these cell lines, probably due to the absence of the methoxy substituent on the enedione structural unit of these indolenaphthoquinones.

Experimental

Unless otherwise indicated, all starting compounds were obtained from commercial suppliers and used without further purification, CH_2Cl_2 was distilled under N_2 from CaH_2. The NMR spectra were recorded on a VXR-300/5 FT-NMR at 300 MHz for ^1H and 75 MHz for ^{13}C or on a Varian Unity Plus 400 MHz FT-NMR for ^1H and 100 MHz for ^{13}C, respectively. *J* Values are given in Hz. Other general experimental procedures are the same as those described previously.[8h]

General procedure for the preparation of β-(1-hydroxybut-3-enyl)indoles 11 and 12

By using a reported procedure for the preparation of β-(1-hydroxy-3-methylbut-3-enyl)indole **5**,[7i] alcohols **11** and **12** could be prepared by the addition of the relevant Grignard reagents into carbonyl compounds **13** and **14**.

β-(1-Hydroxy-2-methylbut-3-enyl)indole 11. Obtained in 95% yield from the reaction of crotylmagnesium bromide with **13** at room temperature for 2 h and further reaction at 45 °C for another 2 h, as a brown gummy product. The ^1H NMR spectrum is complex and the signals could not be fully assigned except for the following; δ_H(300 MHz, $CDCl_3$) 0.92 (3 H, d, *J* 6.9, Me), 2.70–2.88 (1 H, m, 2-H), 4.90–5.40 (3 H, m, 1-H and 4-H_2), 5.80–5.92 (1 H, m, 3-H), 6.89–7.80 (5 H, m, ArH), 7.99 (1 H, br s, NH); *m*/*z* (EI) 201.1161 (M^+; $C_{13}H_{15}NO$ requires 201.1155), 184 (23%), 146 (100) and 117 (19).

β-(1-Hydroxy-1-methylbut-3-enyl)indole 12. Obtained in 96% yield from the reaction of allylmagnesium chloride with 3-acetylindole **14** as a pale yellow solid (Found: C, 77.79; H, 7.61; N, 6.78; $C_{13}H_{15}NO$ requires C, 77.57; H, 7.52; N, 6.96%); mp 70 °C; δ_H(300 MHz, $CDCl_3$) 1.63 (3 H, s, Me), 2.67 (1 H, dd, *J* 8.1 and 13.5, 2-H), 2.82 (1 H, dd, *J* 6.8 and 13.5, 2-H), 5.04 (1 H, d, *J* 10.2, 4-H), 5.09 (1 H, d, *J* 16.8, 4-H), 5.65 (1 H, m, 3-H), 6.87–7.83 (5 H, m, ArH), 8.21 (1 H, br s, NH); δ_C(75 MHz, $CDCl_3$) 28.8, 47.2, 72.0, 111.3, 118.5, 119.2, 120.6, 120.8, 121.7, 122.8, 124.8, 134.2, 136.9; *m*/*z* (EI) 201 (M^+, 5%), 160 (86) and 117 (66).

1-(β-Indolyl)buta-1,3-dienes 2, 25, 26 and 27

A stirred solution of alcohol **5** (1.01 g, 5 mmol) and a catalytic amount of TFA in 100 cm^3 of THF was heated at 50–55 °C for 2 h. The mixture was washed with saturated aqueous $NaHCO_3$ and extracted with diethyl ether. The extract was dried (anhydrous $MgSO_4$) and evaporated to afford the crude product. Rapid chromatography of the freshly obtained product afforded diene **2** (558 mg, 62%), identical with an authentic sample by comparison of spectra data.[7i]

By the same method the acid-catalyzed reaction of **10**[8h] (935 mg, 5 mmol) afforded diene **25** (800 mg, 95%). Alcohol **10** was converted into **26** (*E*/*Z* = 2.5 : 1) in 73% yield as a pale yellow solid. Repeated separation of the mixture by silica gel column yielded a mixture of *cis*- and *trans*-isomers, and the pure *trans*-isomer **26**. Similarly, reaction between **12** and TFA (1.01 g, 5 mmol) afforded diene **27** (687 mg) in 75% yield.

(β-Dehydroprenyl)indole 2. Obtained as a pale yellow solid; mp 127–129 °C; δ_H(300 MHz, $CDCl_3$) 2.01 (3 H, s, Me), 4.98 (1 H, s, 4-H), 5.06 (1 H, s, 4-H), 6.76 (1 H, d, *J* 16.5, 1-H), 6.95 (1 H, d, *J* 16.5, 2-H); *m*/*z* (EI) 183 (M^+, 65%).

1-(β-Indolyl)buta-1,3-diene 25. Obtained as a pale solid; mp 97 °C; ν_{max}(CCl_4)/cm^{-1} 3490, 1636, 1606; δ_H(300 MHz, $CDCl_3$) 5.06 (1 H, dd, *J* 1.2 and 9.9, 4-H), 5.25 (1 H, dd, *J* 1.2 and 16.8, 4-H), 6.53 (1 H, dt, *J* 9.9 and 16.8, 3-H), 6.76 (1 H, d, *J* 15.9, 1-H), 6.84 (1 H, dd, *J* 9.0 and 15.9, 2-H), 7.16–7.90 (5 H, m, ArH), 8.09 (1 H, br s, NH); δ_C(75 MHz, $CDCl_3$) 111.4, 114.6, 115.3, 120.1, 120.4, 122.6, 123.6, 125.5, 125.8, 126.9, 136.8, 138.2; *m*/*z* (EI) 169 (M^+, 57%). The mp and spectral data of **25** were in full agreement with those reported previously.[7b]

(*E*)-1-β-(Indolyl)-2-methylbuta-1,3-diene 26. Obtained as a yellow solid; mp 88 °C; δ_H(300 MHz, $CDCl_3$) 2.04 (3 H, s, Me), 5.07 (1 H, d, *J* 10.5, 4-H), 5.23 (1 H, d, *J* 17.4, 4-H), 6.66 (1 H, dd, *J* 10.5 and 17.4, 3-H), 6.72 (1 H, s, 1-H), 7.12–7.70 (5 H, s, ArH), 8.10 (1 H, br s, NH); δ_C(75 MHz, $CDCl_3$) 13.9, 110.9, 111.0, 114.2, 119.0, 120.0, 122.4, 122.6, 123.1, 127.5, 133.1, 135.5, 142.0; *m*/*z* (EI) 183 (M^+, 87%), 168 (88). The spectral data (^1H NMR, ^{13}C NMR and MS) were in full agreement with those reported.[11]

(*Z*)-1-β-(Indolyl)-2-methylbuta-1,3-diene. The mixture of this compound and its *E*-isomer were obtained as a pale yellow solid; δ_H(300 MHz, $CDCl_3$) 2.06 (3 H, s, Me), 5.14 (1 H, d, *J* 10.8, 4-H), 5.34 (1 H, d, *J* 17.4, 4-H), 6.59 (1 H, s, 1-H), 7.06 (1 H, dd, *J* 10.8 and 17.4, 3-H), 7.11–7.65 (5 H, m, ArH), 8.19 (1 H, br s, NH); δ_C(75 MHz, $CDCl_3$) 20.4, 110.9, 111.0, 114.0, 119.3, 120.9, 122.4, 122.6, 123.5, 127.5, 133.1, 136.0, 142.0. The above spectral data for the *cis*-isomer of **26** were deduced by comparison of those data from a mixture of the two isomers with those of pure *trans*-isomer **26**, and were found to be identical with those reported previously.[11]

(*E*)-1-β-indolyl-1-methylbuta-1,3-diene 27. Obtained as a pale oil in 75% yield; δ_H(300 MHz, $CDCl_3$) 2.19 (3 H, s, Me), 5.11 (1 H, d, *J* 10.8, 2-H), 5.28 (1 H, d, *J* 16.5, 4-H), 6.72 (1 H, d, *J* 10.8, 4-H), 6.81 (1 H, dt, *J* 10.8 and 16.5, 3-H), 7.08–7.98 (6 H, m, ArH), 7.92 (1 H, br s, NH); δ_C(75 MHz, $CDCl_3$) 16.8, 111.4, 115.2, 119.9, 120.2, 120.9, 122.3, 122.7, 125.1, 125.3, 131.7, 133.7, 136.8; *m*/*z* (EI) 183.1059 (M^+, $C_{13}H_{13}N$ requires 183.1049).

General procedure for acid-catalysed reaction of β-(1-hydroxybut-3-enyl)indoles to afford yuehchukene 1 and bisnoryuehchukenes 15a and 15b

A stirred solution of the alcohol **5** and **10** (2 mmol) and a catalytic amount of TFA in 40 cm^3 of THF was heated under reflux for 20 h. Each of the two mixtures was washed with saturated aqueous $NaHCO_3$ and extracted with diethyl ether. The extracts were dried (anhydrous $MgSO_4$) and evaporated to give the crude products. Rapid chromatography of the two freshly obtained products yielded the corresponding yuehchukene **1** (103 mg, 28%) and bisnoryuehchukenes **15a** and **15b**[7b] (4:1) (155 mg, 46%), as a pale gummy solid, and the related bis-indoles **7**[7i] (2 mg) and **16** (2 mg).

Yuehchukene 1. Mp 127 °C; ν_{max}(CCl_4)/cm^{-1} 3400, 2952, 2865, 1450, 740; δ_H(300 MHz, $CDCl_3$) 0.85 (3 H, s, 7-Me), 1.08 (3 H, s, 7-Me), 1.65 (3 H, br s, 9-Me), 2.28 (2 H, AB_q, *J* 16.5, 8-H_2), 3.15 (1 H, dd, *J* 8.4 and 8.4, 6a-H), 4.00 (1 H, m, 10a-H), 4.55 (1 H, d, *J* 8.4, 6-H), 5.67 (1 H, br s, 10-H), 6.95–7.56 (9 H, m, ArH), 7.97 (2 H, br s, 2 × NH); δ_C(75 MHz, $CDCl_3$) 24.1, 28.9, 29.0, 33.5, 37.6, 38.3, 41.0, 60.8, 111.2, 111.7, 118.4, 118.5, 119.3, 119.5, 119.5, 120.5, 120.6, 122.1, 122.3, 122.3, 124.2, 126.8, 130.2, 136.5, 140.2, 145.2; *m*/*z* (EI) 366 (M^+, 100%). The melting point and spectral data of **1** were in full agreement with those reported previously.[1]

Bisnoryuehchukene 15a. δ_H(300 MHz, $CDCl_3$) 1.14 (3 H, d, *J* 6.6, Me), 1.85 (1 H, dd, *J* 4.0 and 17.2, 8-H), 2.09 (1 H, m, 7-H), 2.47 (1 H, ddd, *J* 2.7, 5.0 and 17.4, 8-H), 2.94 (1 H, dd, *J* 7.2 and 12.0, 6a-H), 3.94 (1 H, d, *J* 2.4, 10a-H), 4.57 (1 H, t, *J* 7.2, 6-H), 5.67 (1 H, m, 9-H), 6.08 (1 H, dd, *J* 2.1 and 9.9, 10-H), 7.00 (1 H, d, *J* 2.4, 2′-H), 7.03–7.61 (8 H, m, ArH), 7.71 (1 H, br s, NH), 8.00 (1 H, br s, NH); δ_C(75 MHz, $CDCl_3$) 20.7, 28.5, 29.4, 36.1, 40.0, 58.6, 111.3, 111.7, 117.1, 118.3, 119.3, 119.4, 119.5, 119.6, 120.6, 121.9, 122.1, 123.6, 124.4, 126.6, 128.8, 136.6, 140.4, 144.1; *m*/*z* (EI) 338.1778 (M^+; $C_{24}H_{22}N_2$ requires 338.1783), 323 (17). Mass spectra measured by using a 4:1 mixture of **15a** and **15b**.

(1,1-Di-β-indolyl)but-3-ene 16. Obtained as a pale oil; δ_H(300 MHz, $CDCl_3$) 2.97 (2 H, t, *J* 7.2, CH_2), 4.59 (1 H, t, *J* 7.2, 1-H), 4.94 (1 H, dd, *J* 1.5 and 9.8, 4-H), 5.09 (1 H, dd, *J* 1.8 and 17.1, 4-H), 5.89 (1 H, m, 3-H), 6.92 (2 H, d, *J* 1.8, 2-H), 7.00–7.57 (8 H, m, ArH), 7.80 (2 H, br s, NH); δ_C(75 MHz, $CDCl_3$) 34.1, 40.0, 111.0, 115.5, 119.1, 119.6, 119.7, 121.7, 121.8, 127.0, 136.5, 137.9; *m*/*z* (EI) 286.1475 (M^+; $C_{20}H_{18}N_2$ requires 286.1471), 245 (100%).

General procedure for the acid-catalysed reaction of β-(1-hydroxybut-3-enyl)indoles and β-(1-hydroxyprop-2-enyl)indole 17 to afford bisnoryuehchukene 19 and trinoryuehchukene 20

To a refluxing THF (40 cm^3) solution of alcohol **5** or **10** (1 mmol, for each alcohol) and a catalytic amount of TFA was slowly added a THF (10 cm^3) solution of **17**[8h] (260 mg, 1.5 mmol) over a period of 1 h. By using the above work-up procedure, the crude products of these two reactions were obtained. Rapid chromatography of the two freshly obtained products yielded the corresponding bisnoryuehchukene **19** (18%) and trinoryuehchukene **20** (17%), as pale amorphous solids. The melting points and spectral data of **19** and **20** were in full agreement with those reported previously.[8a,8h]

Bisnoryuehchukene 19. Obtained as a pale solid (61 mg); mp 121 °C (decomp.); δ_H($CDCl_3$) 1.68 (3 H, s, Me), 1.85–1.94 (4 H, m, CH_2CH_2), 3.21 (1 H, m, 6a-H), 3.93 (1 H, m, 10a-H), 4.49 (1 H, d, *J* 7.2, 6-H), 5.80 (1 H, s, 10-H), 6.96 (1 H, d, *J* 2.1, 2′-H), 6.99–7.61 (8 H, m, ArH), 7.69 (1 H, br s, NH), 7.96 (1 H, br s, NH); δ_C($CDCl_3$) 24.1, 24.9, 27.0, 38.3, 39.8, 51.1, 111.3, 111.7, 117.2, 118.4, 119.3, 119.4, 119.6, 120.6, 121.7, 122.2, 123.5, 124.5, 125.5, 126.8, 132.9, 136.7, 140.4, 144.0; *m*/*z* (EI) 338.1789 (M^+; $C_{24}H_{22}N_2$ requires 338.1783).

Trinoryuehchukene 20. Obtained as a pale solid (57 mg); mp 115 °C (decomp.); δ_H(300 MHz, $CDCl_3$) 1.84–2.37 (4 H, m, CH_2CH_2), 3.25 (1 H, m, 6a-H), 3.94 (1 H, m, 10a-H), 4.52 (1 H, d, *J* 7.2, 6-H), 5.80 (1 H, m, 9-H), 6.11 (1 H, m, 10-H), 6.97 (1 H, m, *J* 2.4, 2′-H), 7.00–7.59 (8 H, m, ArH), 7.73 (1 H, br s, NH), 8.00 (1 H, br s, NH); δ_C(75 MHz, $CDCl_3$) 21.9, 24.5, 38.0, 39.9, 51.8, 111.3, 111.7, 117.1, 118.4, 119.3, 119.4, 119.6, 119.6, 120.7, 121.8, 122.2, 124.5, 125.9, 126.8, 129.5, 136.7, 140.5, 144.2; *m*/*z* (EI) 324 (M^+, 100%).

One-pot synthesis of bisnoryuehchukenes 15a and 15b

To a stirred solution of indole-3-carboxaldehyde (145 mg, 1 mmol) in dry THF (10 cm^3) was slowly added allylmagnesium chloride (4 mmol) at room temperature under nitrogen. The mixture was stirred for another 2 h after the addition was complete. An aqueous solution of conc. HCl was added dropwise into the mixture until it was acidic. The stirred mixture was then heated under reflux for 2 h. Water (20 cm^3) was added to the mixture which was then neutralized with saturated aqueous $NaHCO_3$. It was then extracted with dichloromethane. The extract was dried (anhydrous $MgSO_4$) and concentrated. Chromatography of the residue on silica gel afforded a 4:1 mixture of **15a** and **15b** (80 mg, 47%) as a white amorphous solid. The spectral data (^1H NMR, ^{13}C NMR and MS) of **15** were in full agreement with those reported previously.[7b,8h]

Dihydromurrapanine 29 and murrapanine 3

To a stirred solution of alcohol **5** (603 mg, 3 mmol) and methoxyquinone **28a** (455 mg, 3.3 mmol) in 50 cm^3 of THF was added a catalytic amount of TFA at room temperature under an atmosphere of air. After the reaction had proceeded for 12 h, *p*-benzoquinone **28b** (648 mg, 6 mmol) was added. The reaction was continued for another 60 h at room temperature. The mixture was concentrated under reduced pressure. Chromatography of the resulting residue on silica gel and stepwise elution with a mixture of ethyl acetate–hexane (1:5 ⟶ 1:3 ⟶ 1:2) afforded both dihydromurrapanine **29** (142 mg, 15%) and murrapanine **3** (191 mg, 20%). The melting point (278 °C) and spectral data (UV, IR, ^1H NMR, ^{13}C NMR and MS) of **3** were in full agreement with those reported previously.[3,8h]

Dihydromurrapanine 29. Obtained as a brown gummy solid; δ_H(300 MHz, $CDCl_3$) 1.83 (3 H, s, Me), 3.21 (1 H, d, *J* 3.6, 5′-H), 3.22 (1 H, d, *J* 4.2, 5′-H), 3.70 (3 H, s, OMe), 4.95 (1 H, m, 8′-H), 5.66 (1 H, d, *J* 2.7, br s, 7′-H), 5.82 (1 H, s, 3′-H), 7.05–7.49 (5 H, m, ArH), 8.03 (1 H, br s, NH); δ_C(75 MHz, $CDCl_3$) 22.6, 29.3, 32.8, 56.0, 106.8, 111.3, 116.6, 119.3, 119.6, 121.9, 122.5, 123.5, 126.1 128.5, 136.3, 138.8, 139.7, 158.6, 181.1, 187.5; *m*/*z* (EI) 319.1220 (M^+; $C_{20}H_{17}NO_3$ requires 319.1209).

Murrapanine 3. Obtained as a purple solid; mp 278 °C; ν_{max}(MBr)/cm^{-1} 3380, 1678, 1646, 1610, 1594, 1560, 1534, 1216; λ_{max}(MeOH)/nm 221 (ε/dm^3 mol^{-1} cm^{-1} 28 850), 246 (15 850),

282 (17 780), 323 (4780); δ_H(400 MHz, [$^2H_6$]acetone–[$^2H_6$]DMSO, 1:1) 2.48 (3 H, s, Me), 3.84 (3 H, s, OMe), 6.26 (1 H, s, 3′-H), 6.95 (1 H, t, *J* 7.2, 5-H), 7.10 (1 H, t, *J* 7.2, 6-H), 7.18 (1 H, d, *J* 7.2, 7-H), 7.46 (1 H, d, *J* 7.2, 4-H), 7.50 (1 H, d, *J* 1.6, 2-H), 7.54 (1 H, s, 7′-H), 7.84 (1 H, s, 5′-H), 11.15 (1 H, br s, NH); δ_C(100 MHz, [$^2H_6$]acetone–[$^2H_6$]DMSO, 1:1) 20.9, 56.2, 107.9, 111.8, 115.5, 119.0, 119.1, 121.0, 124.5, 125.0, 126.2, 133.7, 136.4, 136.8, 138.3, 138.3, 143.8, 161.5, 178.9, 184.6; *m*/*z* (EI) 317 (M^+, 100%).

Dihydronormurrapanine 32 and normurrapanine 31

By using the same method as described above, **32** (110 mg, 12%) and **31** (183 mg, 20%) were obtained. The melting point and spectral data (UV, IR, ^{1}H NMR, ^{13}C NMR and MS) of **31** were in full agreement with those reported previously.[8h]

Dihydronormurrapanine 32. Obtained as a brown gummy solid; ν_{max}(CCl_4)/cm^{-1} 3410, 1685, 1644, 1612, 1460, 1220; δ_H(300 MHz, $CDCl_3$) 3.28–3.60 (2 H, m, CH_2), 3.68 (3 H, s, OMe), 4.95 (1 H, m, 8′-H), 5.81 (1 H, s, 3′-H), 5.95 (2 H, br s, 6′-H + 7′-H), 7.05–7.58 (5 H, m, ArH), 8.11 (1 H, br s, NH); δ_C(75 MHz, $CDCl_3$) 24.6, 31.5, 56.0, 106.8, 111.3, 116.0, 119.4, 119.5, 120.9, 121.9, 123.7, 126.05, 128.0, 136.3, 138.8, 139.7, 158.5, 181.2, 187.3; *m*/*z* (EI) 305.1046 (M^+; $C_{19}H_{15}NO_3$ requires 305.1053), 303 (93%).

Normurrapanine 31. Obtained as a purple solid; mp 275 °C; ν_{max}(KBr)/cm^{-1} 3348, 1690, 1642, 1614, 1582, 1544, 1210; λ_{max}(MeOH)/nm 220 (ε/dm^3 mol^{-1} cm^{-1} 28 840), 240 (15 850), 277 (17 800), 318 (4180); δ_H(400 MHz, [$^2H_6$]acetone–[$^2H_6$]DMSO, 1:1) 3.83 (3 H, s, Me), 6.32 (1 H, s, 3′-H), 6.96 (1 H, t, *J* 7.6, 5-H), 7.12 (1 H, t, *J* 7.6, 6-H), 7.16 (1 H, d, *J* 7.6, 7-H), 7.45 (1 H, dd, *J* 1.6 and 7.5, 4-H), 7.54 (1 H, d, *J* 2.4, 2-H), 7.75 (1 H, dd, *J* 1.6 and 7.6, 7′-H), 7.80 (1 H, t, *J* 7.6, 6′-H), 8.00 (1 H, dd, *J* 1.6 and 7.6, 5′-H), 11.30 (1 H, br s, NH); δ_C(100 MHz, [$^2H_6$]acetone–[$^2H_6$]DMSO, 1:1) 56.5, 108.1, 111.8, 115.3, 119.1, 119.2, 121.1, 124.4, 124.8, 125.9, 128.4, 133.2, 133.5, 136.3, 136.4, 137.9, 161.4, 179.3, 184.4; *m*/*z* (EI) 303 (M^+, 100%).

Preparation of murrapanine 3 and normurrapanine 31 *via* aerial oxidation in silica gel

To a stirred solution of alcohol **5** (603 mg, 3 mmol) and methoxyquinone **28a** (455 mg, 3.3 mmol) in 50 cm^3 of THF was added a catalytic amount of TFA at room temperature under an air atmosphere. After the reaction had proceeded for 12 h, *p*-benzoquinone **28b** (648 mg, 6 mmol) was added to the reacting mixture, and the reaction was continued for another 24 h. The above mixture was then mixed with 5 g of silica gel and was evaporated to remove THF under reduced pressure. The mixture, absorbed by silica gel, was exposed to the air for 4 days with constant shaking. The mixture was then placed on top of a silica gel column and was eluted stepwise with a mixture of ethyl acetate–hexane (1:5 ⟶ 1:3 ⟶ 1:2) to afford dihydromurrapanine **29** (7 mg, <1%) and murrapanine **3** (535 mg, 56%). Similarly, the reaction of alcohol **10** with quinones **28a** and **28b** by using the above method yielded trace amounts of dihydronormurrapanine **32** and normurrapanine **31** in 31% yield.

Procedure for thermal reaction of alcohols 5 and 10 with *p*-benzoquinone

By using the procedure described previously for the synthesis of **3** and **30**,[8h] 1.0 mmol of the freshly prepared alcohols **5** and **10** were reacted respectively with three equivalents of benzoquinone **28b** at 155 °C for 1 h and led to the isolation of demethoxymurrapanine **33a** and demethoxynormurrapanine **33b** in 26% and 27% yields, respectively.

Demethoxymurrapanine 33a. Obtained as a purple solid (76 mg) (Found: C, 79.31; H, 4.59; N, 4.73; $C_{19}H_{13}NO_2$ requires C, 79.43; H, 4.56; N, 4.87%); mp 247–248 °C; ν_{max}(KBr)/cm^{-1} 3428, 1662, 1610, 1594 and 734; λ_{max}(MeOH)/nm 221 (ε/dm^3 mol^{-1} cm^{-1} 6760), 246 (3890), 286 (1150), 323 (1150); δ_H(400 MHz, [$^2H_6$]acetone–[$^2H_6$]DMSO, 1:1) 2.49 (3 H, s, Me), 6.90 (1 H, d, *J* 10.4, 2′-H or 3′-H), 6.96 (1 H, t, *J* 7.6, 5-H), 7.00 (1 H, d, *J* 10.4, 3′-H or 2′-H), 7.11 (1 H, t, *J* 7.6, 6-H), 7.17 (1 H, d, *J* 8.0, 7-H), 7.46 (1 H, d, *J* 8.0, 4-H), 7.52 (1 H, d, *J* 2.4, 2-H), 7.63 (1 H, s, 7′-H), 7.83 (1 H, s, 5′-H), 11.28 (1 H, br s, NH); δ_C(100 MHz, [$^2H_6$]acetone–[$^2H_6$]DMSO, 1:1) 21.9, 112.7, 116.27, 120.0, 120.1, 122.0, 125.56, 126.3, 127.2, 128.0, 134.4, 137.3, 137.4, 137.4, 139.9, 141.7, 144.5, 185.6, 186.3; *m*/*z* (EI) 287 (M^+, 100%).

Demethoxynormurrapanine 33b. Obtained as a purple solid (74 mg) (Found: C, 79.15; H, 4.10; N, 5.08; $C_{18}H_{11}NO_2$ requires C, 79.11; H, 4.06; N, 5.13%); mp 234–235 °C; ν_{max}(KBr)/cm^{-1} 3404, 1660, 1584 and 738; λ_{max}(MeOH)/nm 223 (ε/dm^3 mol^{-1} cm^{-1} 7410), 245 (3720), 281 (1510), 319 (1120); δ_H(400 MHz, [$^2H_6$]acetone–[$^2H_6$]DMSO, 1:1) 6.95 (1 H, d, *J* 10.4, 2′-H or 3′-H), 6.97 (1 H, t, *J* 7.6, 5-H), 7.04 (1 H, d, *J* 10.4, 3′-H or 2′-H), 7.11 (1 H, t, *J* 7.6, 6-H), 7.20 (1 H, d, *J* 8.0, 7-H), 7.47 (1 H, d, *J* 8.0, 4-H), 7.54 (1 H, d, *J* 2.4, 2-H), 7.81–7.89 (2 H, m, 6′ and 7′-Hs), 8.04 (1 H, dd, *J* 8.0 and 3.6, 5′-H), 11.27 (1 H, br s, NH); δ_C(100 MHz, [$^2H_6$]acetone–[$^2H_6$]DMSO, 1:1) 112.2, 115.6, 119.5, 119.5, 121.4, 125.1, 125.1, 126.4, 129.6, 133.3, 133.8, 136.6, 136.7, 136.9, 138.9, 141.0, 185.3, 185.5; *m*/*z* (EI) 273 (M^+, 100%).

Cytotoxicity testing

Cytotoxicity assays by using a modification of the MTT colorimetric method[14] were carried out according to the procedure described previously.[15]

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