Available online at www.sciencedirect.com

SCIENCE @ DIRECT®

Tetrahedron 60 (2004) 6679–6684

Tetrahedron

Zirconium triflate-catalyzed reactions of indole, 1-methylindole, and pyrrole with α,β-unsaturated ketone

Min Shi,* Shi-Cong Cui and Qing-Jiang Li

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences,
354 Fengli Lu, Shanghai 200032, China

Received 8 May 2004; revised 21 May 2004; accepted 21 May 2004

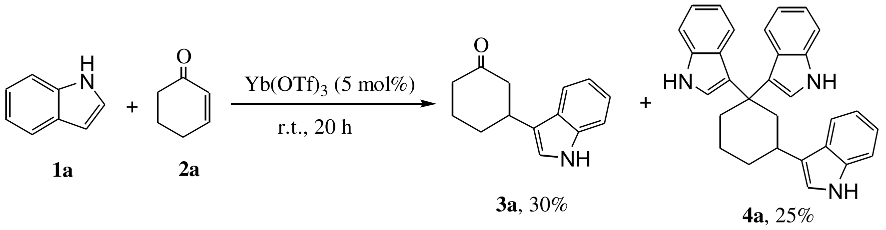
Abstract—The Zr(OTf)$_4$-catalyzed reaction of indole, 1-methylindole or pyrrole with α,β-unsaturated ketone generated the corresponding trisindolyl-, tris(1-methylindolyl-), and trispyrrolylalkanes in moderate to high yields in the mixed solvent EtOH/H$_2$O.

1. Introduction

The Michael addition reaction is one of the most important C–C bond forming reactions in organic chemistry.[1] Recently, many high-yielding, environmentally-benign, oxygen and moisture tolerant Lewis acids such as Ln(OTf)$_3$ (Ln=Yb, Sc, Y, La, etc.) or bismuth nitrate [Bi(NO$_3$)$_3$] have been applied to this transformation.[2] Among them the addition of indole to electron-deficient olefins is a widely investigated process because this reaction is involved in the total synthesis of a class of bioactive indole alkaloids known as the hapalindoles.[2,3] However, in our ongoing investigations of this interesting reaction, we found that this typical Michael addition reaction become complicated in the presence of excess amounts of indoles. For example, in the reaction of indole **1a** (1.5 equiv.) with 2-cyclohexen-1-one **2a** (1.0 equiv.), this reaction produces product **4a** in which three indole moieties have been incorporated, in 25% yield via a 1,4-addition, 1,2-addition and a dehydration process, along with the normal 1,4-addition (Michael addition) product **3a** in 30% yield in the presence of Yb(OTf)$_3$ (5 mol%) under solvent free conditions (Scheme 1).[4] So far the formation of a triindolylalkane has been reported only in the reaction of 1-methylindole with 3-methyl-2-cyclohexene-1-one to give triindolylcyclohexane in low yield as a byproduct under vigorous conditions.[5] Herein, we wish to report this interesting three indole-addition reaction in the presence of various metal triflate Lewis acids under mild conditions.

2. Results and discussion

The promoters for the reaction of indole **1a** (3.0 equiv.) with 2-cyclohexen-1-one **2a** (1.0 equiv.) were systematically examined at first in neat 2-cyclohexen-1-one in the absence of organic solvent. The results are summarized in Table 1. We found that in the reaction of indole **1a** (3.0 equiv.) with 2-cyclohexen-1-one **2a** (1.0 equiv.), the major reaction product was compound **4a** in the presence of various



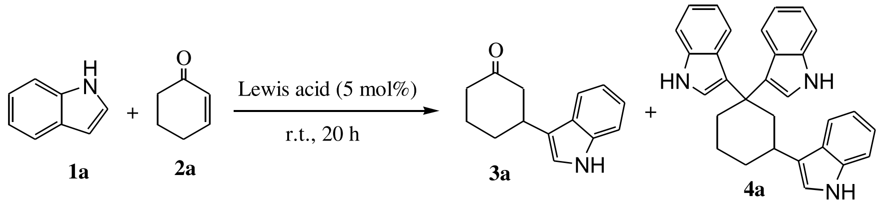
Scheme 1.

Keywords: Indole; Pyrrole; α,β-Unsaturated ketone; Zr(OTf)$_4$; Lewis acid; Michael addition; Trisindolylalkane.

* Corresponding author. Tel.: +86-21-64163300x342; fax: +86-21-64166128; e-mail address: mshi@pub.sioc.ac.cn

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.05.087

Table 1. The reaction indole **1a** (3.0 equiv.) with 2-cyclohexen-1-one **2a** (1.0 equiv.) in the presence of Lewis acid

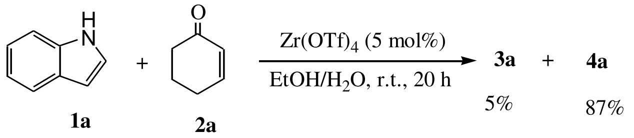


Entry[a]	Lewis acid	Yield [%][b]	
		3a	**4a**
1	$Yb(OTf)_3$	30	43
2	$Sc(OTf)_3$	23	53
3	$Eu(OTf)_3$	26	38
4	$Zr(OTf)_4$	20	60
5	$Hf(OTf)_4$	27	45
6	$Cu(OTf)_2$	27	36
7	$Sn(OTf)_2$	32	36
8	$Ti(OPr^i)_4$	NR	

[a] The reaction was carried out in neat 2-cyclohexene-1one without organic solvent.
[b] Isolated yields.

metal triflate Lewis acids (Table 1, entries 1–7). The Lewis acid $Ti(O^iPr)_4$ showed no catalytic activity for this reaction (Table 1, entry 8). $Zr(OTf)_4$ gave the best result under identical conditions. The three indole-incorporated product **4a** can be isolated in 60% yield under mild conditions using $Zr(OTf)_4$ as a Lewis acid promoter (Table 1, entry 4).

In order to improve the isolated yield of **4a**, solvent effects were examined in various organic solvents in the presence of $Zr(OTf)_4$ (5 mol%). We found that in the mixed polar solvent $EtOH/H_2O$ (2/1), the isolated yield of **4a** can reach 87% in the presence of $Zr(OTf)_4$ (5 mol%) along with 5% of **3a** under mild conditions (Scheme 2).



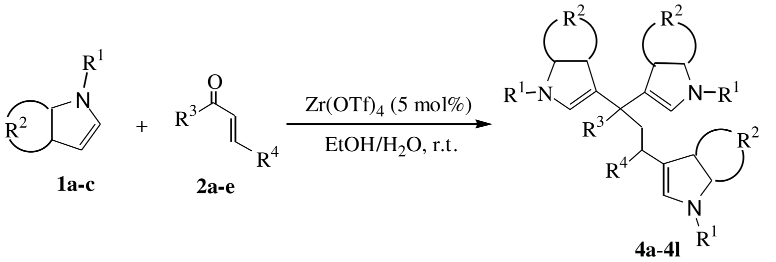
Scheme 2.

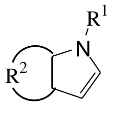
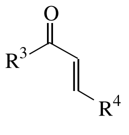
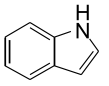
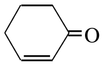
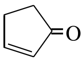
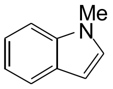
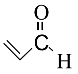
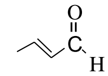
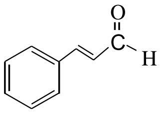
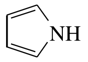
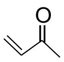
Under these optimized reaction conditions, we next examined the reactions of indole **1a** (5.0 equiv.), 1-methylindole **1b** (5.0 equiv.), pyrrole **1c** (5.0 equiv.) with various α,β-unsaturated ketone (1.0 equiv.) in the presence of $Zr(OTf)_4$ (5 mol%). The results are summarized in Table 2. As can be seen from Table 2, the yields of triindolylalkanes are very sensitive to the substrates employed (Table 2, entries 1–11). Using acrolein **2c**, crotonaldehyde **2d**, *trans*-cinnamaldehyde **2e** as substrates, the corresponding triindolylalkanes **4d**, **4f** and **4h** were produced in moderate to good yields (Table 2, entries 4, 6, and 8). Their yields could be slightly improved by prolonging the reaction time (3 days). For the reaction of indole **1a** with 2-cyclohexene-1-one **2a**, the triindolylalkane **4a** was obtained in 99% yield after 3 days under the same conditions (Table 2, entry 1). For 2-cyclopenten-1-one **2b**, the corresponding triindolylalkane **4b** was obtained in low yield under the same conditions even after a prolonged reaction time (Table 2, entry 2). This may be due to the rigid five-membered ring, which disfavors the 1,4- or 1,2-addition of sterically-demanding indoles in the presence of Lewis acid. On the other hand, using 1-methylindole **1b** to react with 2-cyclohexene-1-one **2a** or crotonaldehyde **2d** under the same conditions, similar results were obtained (Table 2, entries 3 and 7), although in the reaction of **1b** with acrolein **2c** and *trans*-cinnamaldehyde **2e**, the corresponding triindolylalkanes **4e** and **4i** were obtained in lower yields (Table 2, entries 5 and 9). It should be emphasized here that in the case of the reaction of **1b** with **2e**, product **4j** in which two 1-methylindole moieties were incorporated was isolated as a major product in 28% yield (Scheme 3). Using pyrrole **1c** instead of indole, the corresponding tripyrrolylcyclohexane **4k** was formed in 40% under the same conditions (Table 2, entry 10). In addition, the reaction of indole (5.0 equiv.) with methyl vinyl ketone (1.0 equiv.) produced the corresponding triindolylalkane **4l** under the same conditions, although the isolated yield was 8% (Table 2, entry 11).

The mechanism for this three indole or pyrrole incorporating reaction is shown in Scheme 3. The 1,4- and 1,2-additions of indole to α,β-unsaturated ketone take place sequentially to give intermediate **A** in the presence of Lewis acid $Zr(OTf)_4$ (Scheme 3). The dehydration of **A** gives another intermediate **B** which is further activated by Lewis acid $Zr(OTf)_4$ and serves as an electrophile to react with a third molecule of indole, affording intermediate **C**. The corresponding three indole-incorporated product is subsequently formed from intermediate **C** (Scheme 4). We confirmed that product **3a** can be completely transformed to **4a** in the presence of $Zr(OTf)_4$ and indole under the same conditions (Scheme 4). Thus, this result supports the proposed reaction mechanism.

In conclusion, we found that in the reaction of excess amounts of indole, 1-methylindole or pyrrole with

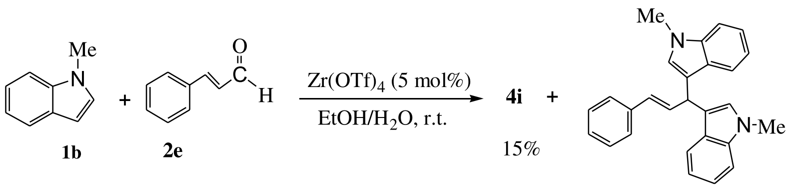
Table 2. Reactions of indole, l-methylindole or pyrrole with α,β-unsaturated ketones in the presence of $Zr(OTf)_4$



Entry[a]					Time/[days]	Yield [%][b], **4a**–**4l**
1		**1a**		**2a**	3	**4a**, 99
2	**1a**			**2b**	3	**4b**, 4
3		**1b**	**2a**		3	**4c**, 80
4	**1a**			**2c**	1 (3)	**4d**, 50 (53)
5	**1b**		**2c**		3	**4e**, 20
6	**1a**			**2d**	1 (3)	**4f**, 60 (61)
7	**1b**		**2d**		3	**4g**, 63
8	**1a**			**2e**	1 (3)	**4h**, 70 (80)
9	**1b**		**2e**		3	**4i**, 15[c]
10		**1c**	**2a**		3	**4k**, 40
11	**1a**			**2f**	3	**4l**, 8

---

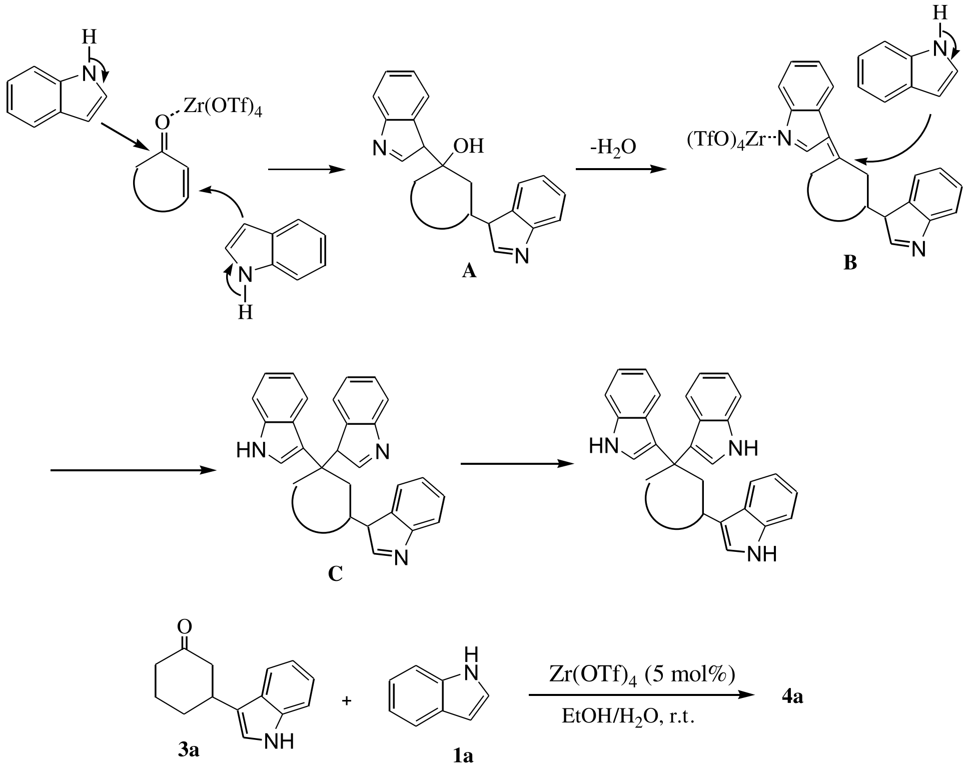
[a] $Zr(OTf)_4$ (5.0 mol%), **1a**–**c** (5.0 equiv.) and α,β-unsaturated ketones (1.0 equiv.) were dissolved in 1.0 mL of EtOH/H_20(2/1) solvent.
[b] Isolated yields.
[c] Anothere product **4j** was isolated in 28% yield.



4j, 28%

Scheme 3.

α,β-unsaturated ketone the trisindolyl- or trispyrrolylalkanes can be produced in the presence of Lewis acid $Zr(OTf)_4$ under mild conditions. Although the isolated yields are highly dependent on the employed substrates, this reaction pathway is interesting and the products obtained are novel. Efforts are underway to elucidate the mechanistic details of this catalytic system and to extend the scope of this interesting reaction.



Scheme 4.

3. Experimental

3.1. General methods

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively. Mass spectra were recorded by EI methods, and HRMS were measured on a Finnigan MA$^+$ mass spectrometer. Organic solvents used were dried by standard methods when necessary. The solid compounds reported in this paper gave satisfactory CHN microanalyses. Commercially available reagents were used without further purification. All reactions were monitored by TLC with Huanghai GF254 silica gel coated plates. Flash column chromatography was carried out using 300–400 mesh silica gel at increased pressure.

A typical reaction procedure for the reaction of indole with 2-cyclohexen-1-one in the presence of Zr(OTf)$_4$. Lewis acid Zr(OTf)$_4$ (5.0 mol%) and indole (292.3 mg, 2.5 mmol) were dissolved in 1.0 mL of EtOH/H$_2$O (2/1) mixed solvent. 2-Cyclohexene-1-one (34.5 mg, 0.5 mmol) was added dropwise into the reaction system by a syringe and the reaction mixture was stirred at room temperature for 3 days. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography to give 1,1,3-tris(3-indolyl)cyclohexane **4a** as a white solid.

3.1.1. 1,1,3-Tris(3-indolyl)cyclohexane 4a. This compound was isolated by flash chromatography to give **4a** as a white solid (eluent: petroleum ether/ethyl acetate=4/1). 212 mg, yield: 99%.

Mp: 217–219 °C; IR (KBr) ν 3470, 3401, 3054, 1456, 1418, 1104 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz, TMS): δ 1.63–1.74 (1H, m, CH$_2$), 1.81–2.02 (2H, m, CH$_2$), 2.15–2.47 (3H, m, CH$_2$), 2.98–3.08 (1H, m, CH), 3.28–3.35 (2H, m, CH$_2$), 6.88–6.92 (3H, m, ArH), 6.96–7.18 (5H, m, ArH), 7.24–7.28 (1H, m, ArH), 7.34 (2H, t, *J*=8.0 Hz, ArH), 7.46 (2H, m, ArH), 7.54 (1H, d, *J*=7.9 Hz, ArH), 7.67 (1H, d, *J*=8.1 Hz, ArH), 7.81 (1H, s, NH), 7.89 (1H, s, NH), 8.11 (1H, s, NH); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 23.3, 31.0, 34.0, 36.6, 40.3, 43.9, 111.1, 111.1, 111.2, 118.5, 118.6, 118.9, 119.4, 119.6, 119.6, 120.4, 120.8, 121.1, 121.2, 121.4, 121.8, 121.9, 122.7, 123.2, 125.8, 126.3, 126.7, 136.3, 137.0, 137.0; MS (EI) *m/z* 429 (M$^+$, 44.19), 312 (M$^+-$117, 90.34), 143 (M$^+-$286, 100). Anal. calcd for $C_{30}H_{33}N_3$: requires C, 83.88; H, 6.34; N, 9.78. Found: C, 83.74; H, 6.21; N, 9.65%.

3.1.2. 1,1,3-Tris(3-indolyl)cyclopropane 4b. This compound was isolated by flash chromatography to give **4b** as a white powder (eluent: petroleum ether/ethyl acetate=4/1). 8.3 mg, yield: 4%.

IR (KBr) ν 3053, 2926, 2854, 1465, 1265 cm^{-1}; ^{1}H NMR (CD$_3$COCD$_3$, 300 MHz, TMS): δ 2.09–2.19 (1H, m, CH$_2$), 2.39–2.78 (3H, m, CH$_2$), 2.91–3.20 (1H, m, CH$_2$), 3.15–3.24 (1H, m, CH$_2$), 3.60–3.74 (1H, m, CH), 6.73–6.80 (2H, m, ArH), 6.90–6.99 (3H, m, ArH), 7.02–7.09 (1H, m, ArH), 7.15–7.17 (1H, m, ArH), 7.29–7.39 (3H, m, ArH), 7.47–7.60 (5H, m, ArH), 9.91 (2H, s, NH), 10.04 (1H, s, NH); MS (EI) *m/z* 415 (M$^+$, 24.23), 298 (M$^+-$117, 87.24), 129 (M$^+-$286, 100); HRMS (EI) calcd for $C_{28}H_{25}N_3$ 415.2049. Found: 415.2034.

3.1.3. 1,1,3-Tris(3-*N*-methylindolyl)cyclohexane 4c. This compound was isolated by flash chromatography to give **4c**

as white crystals (eluent: petroleum ether/ethyl acetate= 4/1). 187 mg, yield: 79%.

Mp: 215–216 °C; IR (KBr): 3054, 2987, 2306, 1712, 1422, 896 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, TMS): δ 1.54–1.69 (1H, m, CH_2), 1.78–1.99 (m, 2H, CH_2), 2.14–2.50 (3H, m, CH_2), 2.92–3.01 (1H, m, CH), 3.20–3.34 (2H, m, CH_2), 3.63 (3H, s, NCH_3), 3.72 (3H, s, NCH_3), 3.86 (3H, s, NCH_3), 6.67 (1H, s, ArH), 6.84 (1H, s, ArH), 6.88–7.32 (m, 10H, ArH), 7.46 (1H, d, *J*=8.0 Hz, ArH), 7.57 (1H, d, *J*=8.0 Hz, ArH), 7.71 (1H, d, *J*=8.0 Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.4, 31.0, 32.5, 32.5, 32.9, 34.3, 36.9, 40.4, 44.3, 109.0, 109.1, 109.2, 117.9, 118.1, 118.3, 118.9, 119.6, 120.7, 120.8, 121.2, 121.3, 121.3, 122.0, 124.4, 125.2, 125.7, 126.1, 127.1, 127.1, 128.0, 137.0, 137.7, 137.7; MS (EI) *m/z* 471 (M^+, 20.08), 340 (M^+-131, 100), 144 (M^+-327, 34.04), 131 (M^+-340, 75.54). Anal calcd for $C_{33}H_{33}N_3$ requires C, 84.04; H, 7.05; N, 8.91. Found: C, 83.60; H, 7.20; N, 8.77%.

3.1.4. 1,1,3-Tris(3-indolyl)propane 4d. This compound was isolated by flash chromatography to give **4d** as a white powder (eluent: petroleum ether/ethyl acetate=4/1). 103 mg, yield: 53%.

IR (KBr) ν 3050, 2920, 2861, 1461, 1260 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, TMS): δ 2.61 (2H, q, *J*=7.3 Hz, CH_2), 2.85 (2H, t, *J*=7.3 Hz, CH_2), 4.56 (1H, t, *J*=7.3 Hz, CH), 6.80–7.33 (12H, m, ArH), 7.49–7.55 (3H, m, ArH), 7.76 (3H, s, NH); MS (EI) *m/z* 389 (M^+, 24.59), 258 (M^+-131, 48.24), 245 (M^+-144, 100); HRMS (EI) calcd for $C_{27}H_{23}N_3$ requires 389.1892. Found: 389.1852.

3.1.5. 1,1,3-Tris(3-*N*-methylindolyl)propane 4e. This compound was isolated by flash chromatography to give **4e** as a white solid (eluent: petroleum ether/ethyl acetate= 4/1). 42 mg, yield: 20%.

Mp: 111–113 °C; IR ($CHCl_3$) ν 3042, 2914, 1604, 1483, 1352, 1328, 1007 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, TMS): δ 2.57–2.67 (2H, m, CH_2), 2.80–2.89 (2H, m, CH_2), 3.71 (3H, s, NCH_3), 3.72 (6H, s, NCH_3), 4.57 (1H, t, *J*=7.4 Hz, CH), 6.78 (1H, s, ArH), 6.88 (2H, s, ArH), 6.98–7.07 (3H, m, ArH), 7.14–7.30 (6H, m, ArH), 7.50 (1H, d, *J*=7.8 Hz, ArH), 7.57 (2H, d, *J*=7.8 Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.8, 32.5, 32.6, 33.6, 36.6, 109.0, 109.0, 115.3, 118.3, 118.4, 118.9, 119.2, 119.8, 121.2, 121.3, 126.0, 126.3, 127.5, 127.9, 137.0, 137.2; MS (EI) *m/z* 431 (M^+, 6.11), 300 (M^+-131, 4.91), 273 (M^+-158, 62.20), 144 (M^+-287, 100), 131 (M^+-300, 56.68); HRMS (MALDI) calcd for $C_{30}H_{29}N_3$+Na 454.2259. Found: 454.2254.

3.1.6. 1,1,3-Tris(3-indolyl)butane 4f. This compound was isolated by flash chromatography to give **4f** as a white solid (eluent: petroleum ether/ethyl acetate=4/1). 123 mg, yield: 61%.

Mp: 108–110 °C; IR (KBr) ν 3056, 2925, 2851, 1460, 1269 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, TMS): δ 1.34 (3H, d, *J*=6.9 Hz, CH_3), 2.31–2.43 (1H, m, CH_2), 2.54–2.67 (1H, m, CH_2), 2.91–3.30 (1H, m, CH), 4.46 (1H, t, *J*= 7.7 Hz, CH), 6.54 (1H, s, NH), 6.59 (1H, s, NH), 6.65 (1H, s, NH), 6.88–7.55 (15H, m, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.8, 28.8, 31.7, 43.6, 111.1, 111.2, 111.2, 118.8, 118.9, 119.5, 119.6, 119.62, 119.9, 120.0, 120.2, 121.5, 121.56, 121.60, 121.63, 121.68, 121.7, 122.2, 126.85, 126.87, 126.89, 136.31, 136.34, 136.4; MS (EI) *m/z* 403 (M^+, 4.14), 245 (M^+-158, 30.78), 84 (M^+-319, 100); HRMS (EI) calcd for $C_{28}H_{25}N_3$ 403.2048. Found: 403.2071 (M^+).

3.1.7. 1,1,3-Tris(3-*N*-methylindolyl)butane 4g. This compound was isolated by flash chromatography to give **4g** as a white solid (eluent: petroleum ether/ethyl acetate=4/1). 140 mg, yield: 63%.

Mp: 115–117 °C; IR (KBr) ν 3050, 2927, 1613, 1483, 1372, 1326, 1013 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, TMS): δ 1.41 (3H, d, *J*=7.1 Hz, CH_3), 2.47 (1H, dt, *J*=7.4 Hz, 13.3 Hz, CH_2), 2.71 (1H, dt, *J*=7.4, 13.3 Hz, CH_2), 3.01–3.15 (1H, m, CH), 3.70 (6H, s, NCH_3), 3.72 (3H, s, NCH_3), 4.55 (1H, t, *J*=7.4 Hz, CH), 6.77 (1H, s, ArH), 6.78 (1H, s, ArH), 6.88 (1H, s, ArH), 6.92–7.04 (3H, m, ArH), 7.12–7.30 (6H, m, ArH), 7.43 (2H, d, *J*=7.8 Hz, ArH), 7.57 (1H, d, *J*=7.8 Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.3, 29.1, 31.9, 32.6, 32.6, 44.5, 109.1, 109.2, 109.3, 118.3, 118.41, 118.42, 119.1, 119.18, 119.18, 119.86, 119.88, 119.95, 121.2, 121.28, 121.32, 121.33, 121.33, 125.2, 126.3, 126.5, 127.3, 127.6, 137.27, 137.34, 137.38; MS (EI) *m/z* 445 (M^+, 15.67), 314 (M^+-131, 10.31), 273 (M^+-172, 100), 159 (M^+-286, 37.89); HRMS (MALDI) calcd for $C_{31}H_{31}N_3$+Na 468.2416. Found: 468.2410.

3.1.8. 1,1,3-Tris(3-indolyl)-3-phenylpropane 4h. This compound was isolated by flash chromatography to give **4h** as a white powder (eluent: petroleum ether/ethyl acetate=4/1). 186 mg, yield: 80%.

Mp: 208–210 °C; IR (KBr) ν 3044, 2920, 2844, 1469, 1257 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, TMS): δ 2.80–2.96 (1H, m, CH_2), 2.99–3.11 (1H, m, CH_2), 4.24 (1H, dd, *J*=10.0, 6.9 Hz, CH), 4.43 (1H, dd, *J*=10.0, 6.9 Hz, CH), 6.81 (1H, d, *J*=2.6 Hz, ArH), 6.88–7.35 (18H, m, ArH), 7.41 (1H, d, *J*=8.4 Hz, ArH), 7.70 (1H, s, NH), 7.88 (1H, s, NH), 7.90 (1H, s, NH); MS (EI) *m/z* 465 (M^+, 2.41), 245 (M^+-220, 100), 207 (M^+-248, 60.18). Anal. calcd for $C_{33}H_{27}N_3$ requires C, 85.13; H, 5.85; N, 9.03. Found: C, 84.86; H, 5.85; N, 8.92%.

3.1.9. 1,1,3-Tris(3-*N*-methylindolyl)-3-phenylpropane 4i. This compound was isolated by flash chromatography to give **4i** as white crystals (eluent: petroleum ether/ethyl acetate=4/1). 39 mg, yield: 15%.

Mp: 222–224 °C; IR (KBr): ν 3052, 2931, 1614, 1484, 1471, 1155, 1013, 1327 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, TMS): δ 2.84–2.95 (1H, m, CH_2), 2.98–3.09 (1H, m, CH_2), 3.65 (3H, s, NCH_3), 3.73 (3H, s, NCH_3), 3.76 (3H, s, NCH_3), 4.25 (1H, dd, *J*=9.4, 6.1 Hz, CH), 4.41 (1H, dd, *J*=9.4, 6.1 Hz, CH), 6.72 (1H, s, ArH), 6.88–7.01 (5H, m, ArH), 7.11–7.34 (13H, m, ArH), 7.43 (1H, dd, *J*=8.0, 0.9 Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 31.3, 32.6, 32.63, 32.7, 40.6, 42.7, 108.9, 109.00, 109.01, 118.0, 118.3, 118.35, 118.43, 118.43, 119.0, 119.43, 119.56, 119.56, 119.8, 120.0, 120.0, 121.19, 121.27, 121.37, 125.88, 125.93, 126.28, 126.41, 127.2, 128.21, 128.23, 137.14, 137.31, 145.4; MS (EI) *m/z* 507 (M^+, 15.46), 376 (M^+-131, 49.35), 273 (M^+-234, 100), 245 (M^+-262, 4.29), 221 (M^+-286, 35.92), 144 (M^+-363, 10.75). Anal calcd for $C_{36}H_{33}N_3$ requires C, 85.17; H, 6.55; N, 8.28. Found: C, 84.88; H, 6.51; N, 8.21%.

3.1.10. [3,3-Bis(3-*N*-methylindolyl)propenyl]benzene 4j. This compound was isolated by flash chromatography to give **4j** as colorless crystals (eluent: petroleum ether/ethyl acetate=10/1). 52 mg, yield: 28%.

Mp: 167–169 °C; IR (KBr) ν 3054, 2929, 2306, 1613, 1469, 1422, 909 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, TMS): δ 3.67 (1H, s, CH), 3.71 (6H, s, NCH_3), 5.39 (1H, d, J=7.1 Hz, CH), 6.49–6.56 (1H, m, CH), 6.74–6.82 (2H, m, ArH), 7.00–7.07 (2H, m, ArH), 7.14–7.38 (9H, m, ArH), 7.60 (2H, d, J=6.9 Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 32.7, 37.3, 109.1, 116.9, 118.7, 120.1, 121.4, 126.3, 126.9, 127.3, 127.34, 128.4, 129.6, 132.8, 137.4, 137.8; MS (EI) *m/z* 376 (M^+, 100), 299 (M^+-77, 13.05), 273 (M^+-103, 46.55), 144 (M^+-232, 25.47), 77 (M^+-299, 9.24). Anal calcd for $C_{36}H_{33}N_3$ requires C, 86.13; H, 6.43; N, 7.44. Found: C, 86.33; H, 6.41; N, 7.43%.

3.1.11. 1,1,3-Tris(2-pyrolyl)cyclohexane 4k. This compound was isolated by flash chromatography to give **4k** as a yellowish oil (eluent: petroleum ether/ethyl acetate=4/1). 56 mg, yield: 40%.

Mp: 189–191 °C; IR (KBr) ν 3043, 2921, 2866, 1478, 1258 cm^{-1}; ^1H NMR (CD_3COCD_3, 300 MHz, TMS): δ 1.55–1.77 (2H, m, CH_2), 1.78–2.01 (4H, m, CH_2), 2.58 (1H, d, J=13.7 Hz, CH), 2.74–2.91 (2H, m, CH_2), 5.69–6.17 (6H, m, ArH), 6.49–6.72 (3H, m, ArH), 9.32 (1H, s, NH), 9.83 (1H, s, NH), 9.94 (1H, s, NH); MS (EI) *m/z* 279 (M^+, 100), 212 (M^+-67, 58.54), 145 (M^+-134, 36.61); HRMS (EI) calcd for $C_{18}H_{21}N_3$ requires 279.1735. Found: 279.1741.

3.1.12. 2,2,4-Tris(3-indolyl)butane 4l. This compound was isolated by flash chromatography to give **4l** as s white solid (eluent: petroleum ether/ethyl acetate=4/1). 16 mg, yield: 8%.

Mp: 155–157 °C; IR (KBr) ν 3053, 2926, 2854, 1465, 1265 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, TMS): δ 2.00 (3H, s, CH_3), 2.60 (2H, t, J=8.6 Hz, CH_2), 2.80 (2H, t, J=8.6 Hz, CH_2), 6.81–7.18 (9H, m, ArH), 7.31 (4H, t, J=7.3 Hz, ArH), 7.41 (2H, d, J=8.4 Hz, ArH), 7.84 (1H, s, NH), 7.97 (2H, s, NH); MS (EI) *m/z* 403 (M^+, 15.08), 259 (M^+-144, 100). Anal. calcd for $C_{28}H_{25}N_3$ requires C, 83.34; H, 6.29; N, 10.41. Found: C, 83.31; H, 6.19; N, 10.27%.

Acknowledgements

We thank the State Key Project of Basic Research (Project 973) (No. G2000048007), Chinese Academy of Sciences (KGCX2-210-01), Shanghai Municipal Committee of Science and Technology, and the National Natural Science Foundation of China for financial support (20025206, 20390050, and 20272069).

References and notes

1. Bull, S. D.; Davies, S. G.; Delgado-Ballester, S.; Fenton, G.; Kelly, P. M.; Smith, A. D. *Synlett* **2000**, 1257–1258. (b) Davies, S. G.; McCarthy, T. D. *Synlett* **1995**, 700–701. (c) Rosenthal, D.; Braundrup, G.; Davis, K. H.; Wall, M. E. *J. Org. Chem.* **1965**, *30*, 3689–3693. (d) Pushechnikov, O.; Ivonin, S. P.; Chaikovskaya, A. A.; Kudrya, T. N. *Chem. Heterocycl. Compd.* **1999**, *35*, 1313–1318.
2. Harrington, P. E.; Kerr, M. A. *Can. J. Chem.* **1998**, *76*, 1256–1265. (b) Kotsuki, H.; Teraguchi, M.; Shimomoto, N.; Ochi, M. *Tetrahedron Lett.* **2002**, *43*, 4075–4078. (c) Harrington, P. E.; Kerr, M. A. *Synlett* **1996**, 1047–1048. (d) Srivastava, N.; Banik, B. K. *J. Org. Chem.* **2003**, *68*, 2109–2117. (e) Chakrabarty, M.; Ghosh, N.; Basak, R.; Harigaya, Y. *Tetrahedron Lett.* **2002**, *43*, 4075–4078. (f) Banerji, J.; Dutta, U.; Basak, B.; Saha, M.; Budzikiewicz, H.; Chatterjee, A. *Indian. Chem. Sect., B* **2001**, *40*, 981–984. (g) Yadav, J. S.; Reddy, B. V.; Subba, M. Ch. V. S. R.; Kumar, G. M.; Madan, C. *Synthesis* **2001**, *5*, 783–787.
3. These cytotoxic compounds are a class of at least 20 members isolated from the blue-green algae *Hapalosiphon fontinalis* by Moore and co-workers. (a) Moore, R. E.; Cheuk, C.; Yang, X.-Q.; Patterson, G. M. L.; Bonjouklian, R.; Smitka, T. A.; Mynderse, J.; Foster, R. S.; Jones, N. D.; Swartzendruber, J. K.; Deeter, J. B. *J. Org. Chem.* **1987**, *52*, 1036–1041. (b) Moore, R. E.; Cheuk, C.; Patterson, G. M. L. *J. Am. Chem. Soc.* **1984**, *106*, 6456–6457.
4. Wang and co-workers reported the 1,2-addition of indole to cyclohexanone accompanied with dehydration to give a two indole-incorporated product Chen, D.; Yu, L.; Wang, P. G. *Tetrahedron Lett.* **1996**, *37*, 4467–4470.
5. Kerr reported that under ultra high pressure (13 kbar) trisindolylcyclohexane was formed in 6% in the reaction of 1-methylindole with 3-methyl-2-cyclohexene-1-one[2a].