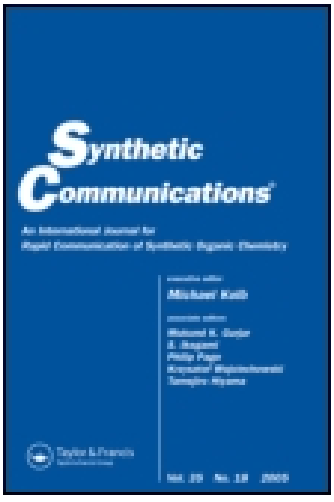

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Synthesis of Novel *Murrapanine* Analogues by Microwave Irradiation

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Abstract: Some new *Murrapanine* analogues have been synthesized via microwave irradiation by intermolecular Diels–Alder cyclization of 1-tosyl-3-(3-methyl-1,3-vinylallyl) indole with a dienophile such as quinone. The structure of the compounds has been characterized by ^{1}H NMR and MS.

Keywords: Synthesis, *murrapanine* analogues, microwave irradiation

The genus *Murraya paniculata* of the plant family *Rutacaea* occurs throughout tropical and subtropical areas. Certain *Murraya* species in Taiwan were known to have a new skeletal cytotoxic indole-naphthoquinone alkaloid, *murrapanine*, with high anticancer activity.[1] In the human nasopharyngeal

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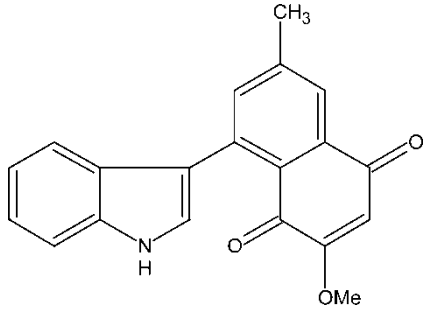
epidermoid carcinoma cell (KB) tissue culture assay, *murrapanine* demonstrated significant cytotoxicity ($ED_{50} = 3.3\,\mu g/mL$).[1]

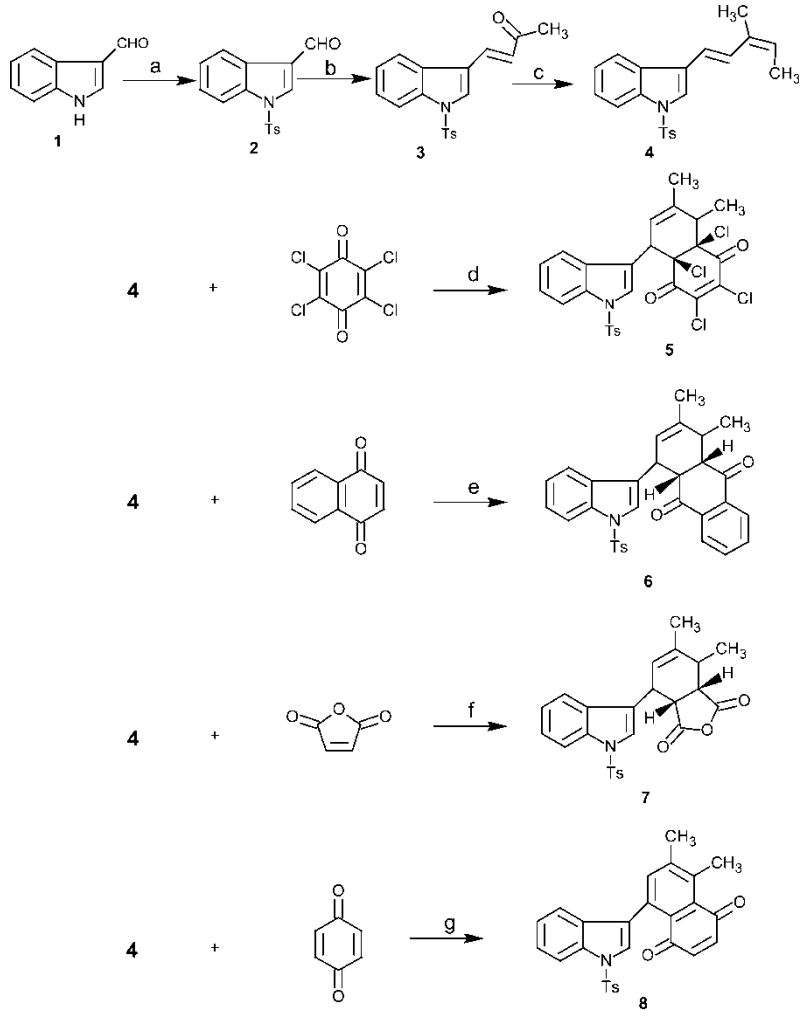


Murrapanine

In biogenesis, there were derivative procedures of *murrapanine* that were similar to 3-dehydroprenylindole via a Diels–Alder [4n + 2] reaction to afford indole derivatives. They have been synthesized by biomimetic synthesis.[1–3] A few years ago, the research showed that the compounds with indole or isoindole groups exhibit anticancer activity.[4–7] To test the effect of *murrapanine* analogues in bioactivity and to find new compounds with excellent anticancer and antiinflammatory activities, we synthesized four novel *murrapanine* analogues. The synthesis of these is summarized in Scheme 1. The indole-3-aldehyde **1** was tosylated to yield **2** and then condensed with acetone to give **3**. The key intermediate **4** was obtained by Wittig reaction of α,β-unsaturated ketone **3** with ethyltriphenylphosphonium bromide. Cyclization of **4** with dienophile via a Diels–Alder [4n + 2] reaction by conventional heating[8–11] or microwave irradiation afforded compounds **5**–**8**.

1. RESULTS AND DISCUSSION

The conventional heating is conduction heating by thermal radiation of outside heat source from outside to inside, so that the rate of energy utilization was low and the distribution of energy wasn't homogeneous. When the solution was irradiated by microwave, the polar molecules of solution simultaneously absorbed and transmitted energy, so the rate of heating was quick and the energy of solution from outside to inside was homogeneous. This was the systemic heating that was homogeneous and efficient by microwave irradiation. The Arrhenius equation (index relation) between most of the chemical reaction rate and temperature, shared that the rate of reaction rose highly by microwave irradiation.[12] The Diels-Alder reaction is a certain cycloaddition of [4n + 2]; compared with the conventional heating, the microwave irradiation might obviously shorten reaction time and increase the rate of production.[13] The results are reported in Table 1.



Scheme 1. Synthesis line of compounds **5**–**8**: (a) $TsCl/Et_2O$–20% NaOH/5–10°C; (b) CH_3COCH_3–10% NaOH/r.t.; (c) $Ph_3PethylBr$–*n*-BuLi–THF; (d) C_6H_6/microwave or C_6H_6/80°C; (e) DMSO/microwave or PhMe/120°C; (f) PhMe/microwave or C_6H_6/80°C; (g) DMSO/microwave or C_6H_6/80°C.

When compound **8** was synthesized, the reaction was performed on intermediate **4** with 1,4-benzoquinone in the light of a molar ratio of 1 : 1. 1,4-Benzoquinone was consumed completely at the moment, but **4** remained unchanged. Until the reaction of intermediate **4** with 1,4-benzoquinone was near the molar ratio of 1 : 3, the two reactants were consumed completely. The cause might be that the Diels–Alder reaction product was oxidized

Table 1. Comparison of synthesis of **5**, **6**, **7**, and **8** between conventional heating and microwave irradiation

	Conventional heating		Microwave irradiation	
Compound	Time, h	Yield, %	Time, min	Yield, %
5	24	18	20	22
6	16	18	20	20
7	12	36	20	38
8	72	33	20	42

to a more stable aromatized product **8** by 1,4-benzoquinone due to the electron-donating effect of two methyl groups. 1,4-Benzoquinone was reduced to hydroquinone, and quinhydrones were formed by hydroquinone with 1,4-benzoquinone. The amount of by-products of microwave irradiation were less than with conventional heating in the reaction, and therefore the yield was obviously increased.

Although some new *murrapanine* analogues could be prepared easily with these two methods, a substantial amount of intractable mixtures was also obtained as red gummy materials in these reactions, rendering decreased yields of the desired compounds. The important feature of the Diels–Alder reaction was high stereoselectivity, and the original steric structure of diene and dienophile was not changed.[14] In this article, because the substituent groups of dienophiles (chloranil, naphthoquinone, maleic anh1,4-benzoquinone) were *cis* structure, these substituent groups in additive products were still *cis*. In other words, the desired compounds were *cis*-configuration.

2. EXPERIMENTAL

^{1}H NMR spectra were recorded on a Bruker AV-300 (300-MHz) spectrometer with tetramethylsilane as an internal standard, and the chemical shifts were expressed in δ values. Mass spectra were obtained with a Shimadzu QP-5000 spectrometer. Melting points were determined on a XT-4 micro-melting-point apparatus and are uncorrected. Microwave reactions were carried out in Galanz WP700 microwave oven. TLC was used for monitoring the reaction, and preparative TLC was performed on silica gel GF 254 (Yantai Yuanbo Silica Gel Co. Ltd. of China). Column chromatography was performed on silica gel of 200–300 mesh (Yantai Yuanbo Silica Gel Co. Ltd. of China).

Ethyltriphenylphosphonium bromide was prepared from bromoethane and triphenylphosphine.[15]

2.1. 1-Tosyl-indole-3-aldehyde (2)

A mixture of indole-3-aldehyde (**1**) (1.45 g, 10 mmol), *p*-toluenesulfonyl chloride (2.48 g, 13 mmol), and 20% aqueous sodium hydroxide (10 mL) in ether (100 mL) was stirred at 5–10°C for 20 h. The mixture was poured into water, and the organic layer was separated. The aqueous layer was extracted with additional ether, and the combined organic layer was washed with sodium chloride solution, saturated, and dried. Evaporation of the solvent gave a residue, which was recrystallized by ethyl acetate afforded **2** (2.77 g, 92%) as light-yellow crystals: mp 143–145°C (lit.[4] 148–150°C); ^{1}H NMR δ 2.38 (s, 3H, Ph-CH_3), 7.26–7.84 (m, 5H, indole-H), 7.86–8.26 (m, 4H, Ph-H), 10.09 (s, 1H, CHO); MS m/z (%) 299 (M^+, 58), 155 (58), 116 (18), 91 (100).

2.2. 1-Tosyl-3-(1-methyl vinyl ketone-3) Indole (3)

A solution of 1-tosyl-indole-3-aldehyde (**2**) (2.99 g, 10 mmol), acetone (50 mL), and 10 % aqueous sodium hydroxide (10 mL) was stirred at room temperature for 3 h. Then most of the solvent was removed on a rotary evaporator until a slurry resulted; the slurry was poured into water and extracted with methylene dichloride. The solvent was evaporated off, and the residue was purified by column chromatography using elution with petroleum ether/methylene dichloride/tetrahydrofuran/ethyl acetate (12 : 5 : 2 : 1), which gave **3** (2.14 g, 63%) as yellow crystals: mp 110–112°C (lit.[4] 109–111°C); ^{1}H NMR δ 2.35 (s, 3H, $PhCH_3$), 2.38 (s, 3H, $COCH_3$), 6.84 (d, $J = 16.3$ Hz, 1H, C═CHCO), 7.60 (d, $J = 16.3$ Hz, 1H, indole-CH═C), 7.24–7.99 (m, 9H, Ar-H); MS m/z (%) 339 (M^+, 45), 324 (7), 184 (100), 155 (30), 91 (90), 65 (62), 43 (73).

2.3. 1-Tosyl-3-(3-methyl-1,3-vinylallyl) Indole (4)

A three-necked, round-bottomed flask equipped with a pressure-equalizing dropping funnel was charged with ethyltriphenylphosphonium bromide (390 mg, 1.05 mmol) and tetrahydrofuran (1 mL) that was distilled from sodium–benzophenone ketyl and was flushed with nitrogen. The system was cooled in an ice bath and a positive pressure of nitrogen, and butyllithium (0.42 mL, 2.5 M) was added dropwise. Then the ice bath was removed, and after the reaction mixture was stirred at room temperature for 30 min, **3** (339 mg, 1 mmol) in tetrahydrofuran was added dropwise. The reaction mixture was stirred at room temperature for 18 h, poured into water, and extracted with ether. The extract was dried over anhydrous sodium sulfate, evaporated, and subjected to chromatography on silica gel (GF 254, petroleum ether/acetone 4 : 1) to give 261 mg of **4** (a small amount of **4**

was transformed to other compounds due to its unstable character). Begin the following reaction at once!

2.4. 2,3,4a,8a-Tetrachloro-7,8-dimethyl-5-(1-tosylindole-3-yl)-4a,5,8,8a-tetrahydro-1,4-naphthoquinone (5)

A solution of **4** (261 mg, 0.7 mmol), benzene (20 mL), and chloranil (490 mg, 2 mmol) was taken in an Erlenmeyer flask and placed in a microwave oven. The solution was irradiated at 280 W for 20 min. Then the solvent was removed in a rotary evaporator, and the residue was separated by column chromatography (silica gel, petroleum ether/acetone 4 : 1) to give **5** (130 mg, two steps, yield was 22%) as yellow powder: mp 190–192°C; ^{1}H NMR ($CDCl_3$) δ 1.60 (d, $J = 7.5$ Hz, 3H, 8-CH_3), 2.01 (s, 3H, 7-CH_3), 2.38 (s, 3H, Ph-CH_3), 3.49 (m, 1H, 8-H), 4.57 (m, 1H, 5-H), 5.51 (m, 1H, 6-H), 7.03–7.91 (m, 9H, Ar-H), MS m/z (%) 597 (8), 595 (M^+, 5), 560 (7), 525 (11), 368 (10), 351 (10), 196 (37), 181 (18), 155 (15), 116 (12), 91 (100), 65 (42), 44 (66).

2.5. 1-(1-Tosylindole-3-yl)-3,4-dimethyl-1,4,4a,9a-tetrahydro-antraquinone (6)

A solution of **4** (261 mg, 0.7 mmol), dimethyl sulfoxide (15 mL), and naphthoquinone (112 mg, 0.7 mmol) was taken in an Erlenmeyer flask and placed in a microwave oven. The solution was irradiated at 119 W for 20 min, poured into water, and extracted with ethyl acetate. The extract was dried and evaporated; the residue was chromatographed on silica gel to give **6** (101 mg, two steps, yield was 20%) as light yellow powder: mp 167–169°C; ^{1}H NMR ($CDCl_3$) δ 1.40 (d, $J = 7.5$ Hz, 3H, 4-CH_3), 1.95 (s, 3H, 3-CH_3), 2.40 (s, 3H, Ph-CH_3), 2.63 (m, 1H, 4-H), 3.41 (t, 1H, 4a-H), 3.71 (t, 1H, 9a-H), 4.11 (m, 1H, 1-H), 5.58 (brs, 1H, 2-H), 7.09–7.79 (m, 13H, Ar-H); MS m/z (%) 509 (M^+, 5), 449 (39), 223 (33), 238 (14), 196 (79), 181 (46), 116 (20), 91 (100), 65 (52), 44 (42).

2.6. 5,6-Dimethyl-3-(1-tosylindole-3-yl)cyclohex-4-ene-1,2-dicarbox-ylic Anhydride (7)

A solution of **4** (261 mg, 0.7 mmol), dried toluene (15 mL), and maleic anhydride (70 mg, 0.7 mmol) was taken in an Erlenmeyer flask and placed in a microwave oven. The solution was irradiated at 462 W for 20 min. The solvent was removed, and the residue was recrystallized by toluene and sulfuric ether to give **7** (170 mg, two steps, yield was 38%) as light-yellow granular crystal: mp 191–193°C; ^{1}H NMR ($CDCl_3$) δ 1.58 (d, $J = 7.2$ Hz,

3H, 6-CH_3), 1.88 (s, 3H, 5-CH_3), 2.32 (s, 3H, Ph-CH_3), 2.74 (m, 1H, 6-H), 3.40–3.62 (m, 2H, 1-H, 2-H), 3.80 (brs, 1H, 3-H), 6.01 (brs, 1H, 4-H), 7.21–7.96 (m, 9H, Ar-H); MS m/z (%) 449 (M^+, 14), 351 (7), 222 (9), 206 (10), 196 (100), 181 (54), 116 (38), 91 (97), 65 (54), 39 (35).

2.7. 5-(1-Tosylindole-3-yl)-7,8-dimethyl-1,4-naphthoquinone (8)

A solution of **4** (261 mg, 0.7 mmol), dimethyl sulfoxide (15 mL), and 1,4-benzoquinone (228 mg, 2.1 mmol) was taken in an Erlenmeyer flask and placed in a microwave oven. The solution was irradiated at 119 W for 20 min, poured into water, and extracted with ethyl acetate. The extract was dried, evaporated, and separated by column chromatography (silica gel, petroleum ether/acetone 4 : 1) to give **8** (190 mg, two steps, yield was 42%) as orange-yellow powder: mp 208–210°C; ^{1}H NMR ($CDCl_3$) δ 2.36 (s, 3H, Ph-CH_3), 2.45 (s, 3H, 7-CH_3), 2.71 (s, 3H, 8-CH_3), 6.70, 6.84 each (d, $J = 10.2$ Hz, 1H, 1,4-benzoquinone-H), 7.41 (s, 1H, 6-H), 7.04–7.99 (m, 9H, Ar-H); MS m/z (%) 455 (M^+, 16), 300 (100), 91 (31), 65 (20), 44 (68).

Compounds **5**–**8** have been synthesized by 1-tosyl-3-(3-methyl-1,3-vinylallyl) indole (**4**) with dienophile (chloranil, naphthoquinone, maleic anhydride, 1,4-benzoquinone) in benzene or toluene via conventional heating. Their yields were described in Table 1.

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REFERENCES

1. Wu, T. S.; Liou, M. J.; Lee, C. J. *Tetrahedron Lett.* **1989**, *30*, 6649.
2. Xie, J. X.; Xie, L.; Gu, Z. P. *Acta Pharmaceutica Sinica* **1988**, *23* (10), 732 (in Chinese).
3. Xu, L.; Liu, J.; Xu, S. P. *Acta Pharmaceutica Sinica* **2001**, *36* (1), 29 (in Chinese).
4. Wattenberg, L. W. *Cancer Res.* **1983**, *43* (5, suppl.), 2448.
5. Takuji, T.; Toshihiro, K.; Yukio, M. *Jpn. J. Cancer Res.* **1992**, *83* (8), 835.
6. Takahashi, N.; Sresser, D. M.; Williams, D. E. *Food Chem. Toxicol.* **1995**, *33* (10), 841.
7. El-Bayoumy, K.; Upadhyaya, P.; Desei, D. H. *Anticancer Res.* **1996**, *16* (5A), 2709.
8. Kin-Far, C.; Tin-Yau, C. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1555.
9. Anthony, P.; Guzikonski; Cai, S. X. *J. Med. Chem.* **1996**, *39*, 4643.
10. Kenji, H.; Kaoru, U.; Ken, K. *J. Chem. Soc., Chem. Commun.* **1984**, 71.

11. Wenkert, E.; Moeller, P. D. R.; Piettre, S. R. *J. Org. Chem.* **1988**, *53* (14), 3170.
12. Xue, Y. Q.; Wang, Z. Z.; Zhang, R. *The Method and Technology of Modern Organic Synthesis*; Chemical Industry Press: Beijing, 2003; pp. 278–279.
13. Wang, J.; Jiang, F. C. *Chin. J. Org. Chem.* **2002**, *22* (3), 212.
14. Wang, B. R. *Organic Synthesis Reaction*; Science Press: Beijing, 1981; pp. 453–455.
15. Li, L. Z.; Lin, Y.; Song, Y. L.; Yuan, J. F.; Tang, K. L. *The Principle and Technology of Organic Synthesis*; Higher Education Press: Beijing, 1992; p. 88.