Synthesis of a New Class of Spirophenanthrones

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Abstract: Using 5 mol% of proline as a recoverable catalyst, 9-phenanthrols react with formaldehyde at room temperature, through Mannich bases and 10-methylene-9-phenanthrone intermediates, to form a new class of spirophenanthrones.

Key words: polymethoxyaromatics, Mannich bases, hetero Diels–Alder reaction, 10-methylene-9-phenanthrone, dimerization

Several groups of natural products with polymethoxyaromatic structure are known to have important biological activities.[1–4] Recently, we are interested in a new class of polymethoxyaromatics **1** (Figure 1) with a spiro structure. Herein we wish to report a new synthesis of these spirophenanthrones in combination with an efficient one-pot phenanthrol synthesis.

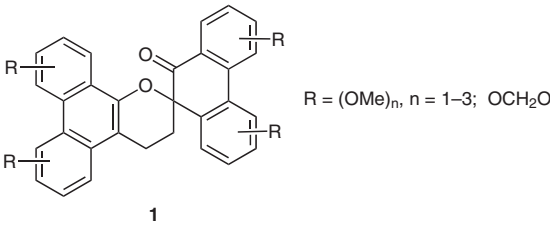
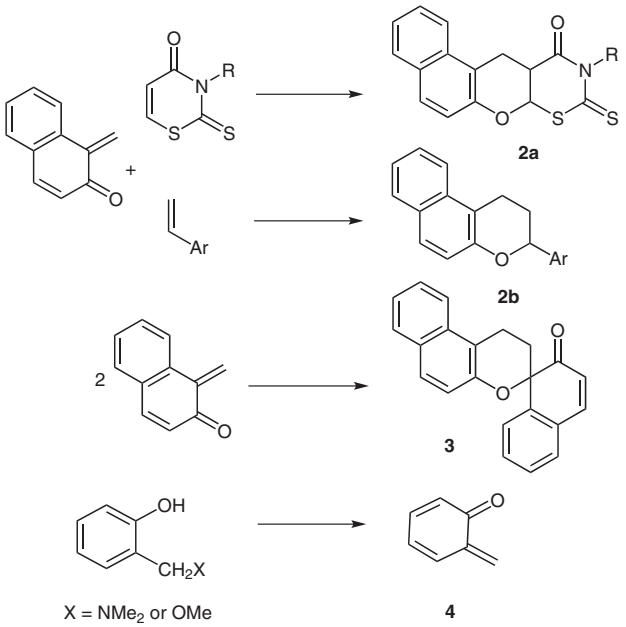


Figure 1

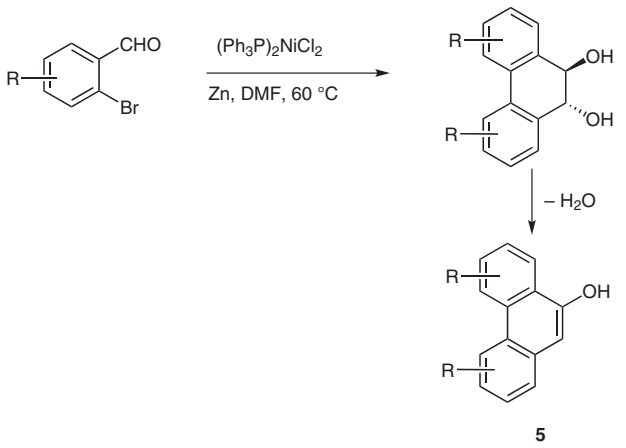
Recently, Bilgic and Mohinder found that *o*-quinone methide precursor reacted with 1,3-thiazine or substituted styrenes via the Diels–Alder reaction to give chroman derivatives **2a** and **2b**,[5] On the other hand, 1,2-naphthoquinone-1-methide dimerized to form a spirodimer **3**.[6] We also found that *o*-quinone methide **4** could be prepared from *o*-dimethylaminomethylphenol or *o*-methoxymethylphenol (Scheme 1).[7]

Based on these previous reports, we present here a convenient and efficient synthetic approach of spirophenanthrone **1**. In this approach, 9-phenanthrol **5** was used as a precursor. Compound **5** was prepared from *o*-bromobenzaldehyde using the method developed by our group (Scheme 2).[8]

Condensation of **5** with formaldehyde catalyzed by proline at room temperature gave directly the target product spirophenanthrone **1**. The substrate 9-phenanthrol **5** first underwent a Mannich reaction affording the expected



Scheme 1



Scheme 2 Synthesis of 9-phenanthrols

Mannich base **6**, which proved to be very unstable. Elimination of proline then produced the 10-methylene-9-phenanthrone intermediate **7** which was highly reactive and readily dimerized via a hetero Diels–Alder reaction (Scheme 3).

The Mannich reaction and the subsequent decomposition of the Mannich base were both promoted by acids and the Mannich reaction also required the participation of a secondary amine, thus a catalytic quantity of proline was

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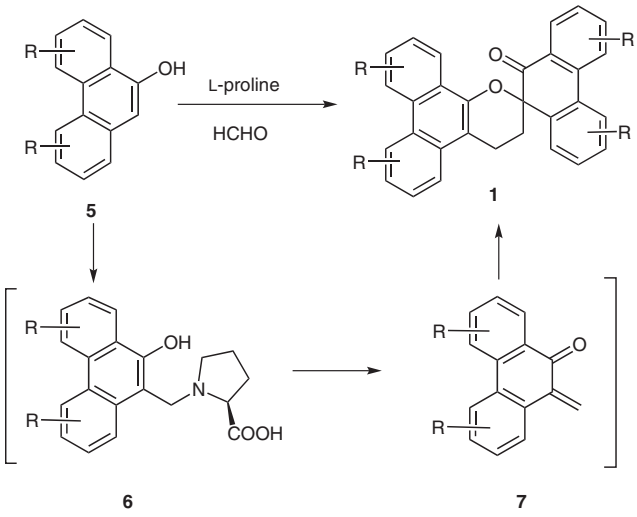


Scheme 3 Synthesis of spirophenanthrones

used as the promoter which served both as a secondary amine and an acidic catalysis. With this promoter, the entire reaction could be completed within 2–4 hours at room temperature and reasonable yields (60–85%) were obtained. Moreover, the proline could be recovered expediently.

For a better understanding of the scope and efficiency of above reactions, various substituted 9-phenanthrols were tested (Table 1).[10] As shown in Table 1, when the substituent was electron donating, moderate to good yield was obtained (entries 1–5). Among these substrates, 2,3,4,5,6,7-hexamethoxyl-9-phenanthrol gave the highest yield (85%, entry 1).When the substituent was electron withdrawing, the yield decreased (entry 7). This was due to the fact that the Mannich reaction occurred more readily with electron-rich aromatic rings. An unexpected result was found from picen-13-ol substrate (entry 8), from which no expected product was obtained. This might be due to its highly steric hindrance.

Table 1 Results of the Synthesis of the Dimers of 10-Methylene-9-phenanthrones[9,10]

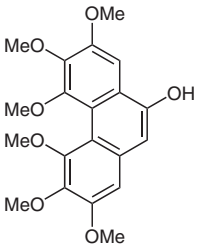
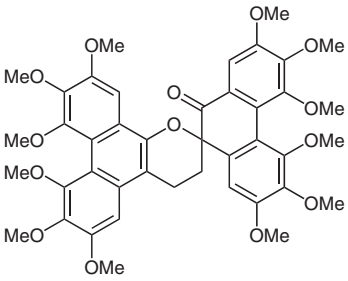
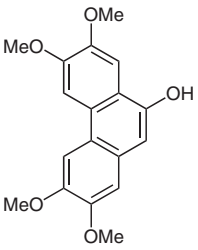
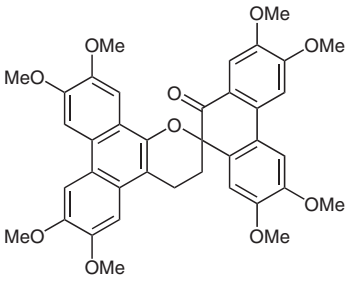
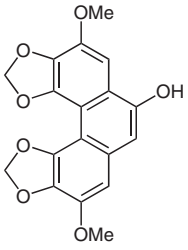
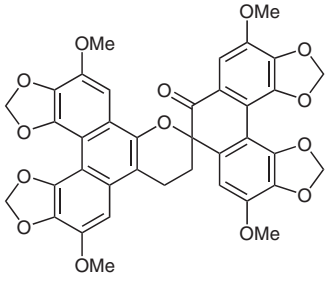
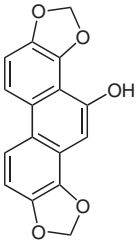
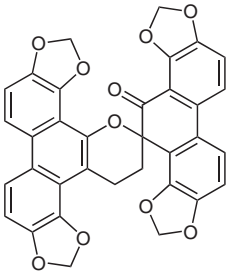
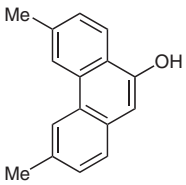
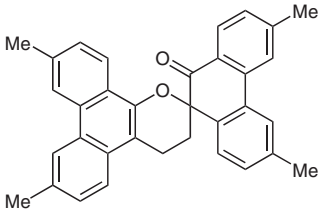
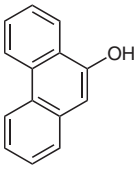
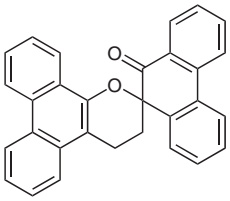
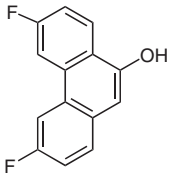
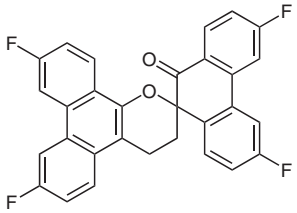
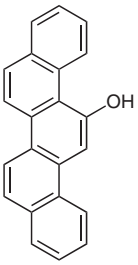
Entry	Substrate	Product	Isolated yield (%)
1	 **5a**	 **1a**	85
2	 **5b**	 **1b**	82
3	 **5c**	 **1c**	79

Table 1 Results of the Synthesis of the Dimers of 10-Methylene-9-phenanthrones[9,10] (continued)

Entry	Substrate	Product	Isolated yield (%)
4	 **5d**	 **1d**	65
5	 **5e**	 **1e**	67
6	 **5f**	 **1f**	60
7	 **5g**	 **1g**	31
8	 **5h**	no reaction	–

10-Methylene-9-phenanthrone may react in either a dipolar form (**8**) or a diradical form (**9**).[6] In the ^{1}H NMR signals of compound **1a–g**, the methylene protons in the dihydropyran ring appear as four trebles of doublets at δ = 2.1–3.2 ppm. This can support the [4+2] cycloaddition process as the mode A and indicates a diradical mechanism[6] (Figure 2).

Although the catalyst proline used in the reaction was levorotatory, all products formed were racemic. A byproduct **10** could also been isolated, and its structure was identified (Scheme 4). Presumably, this compound was formed by Michael addition of 9-phenanthrol to10-methylene-9-phenanthrone.

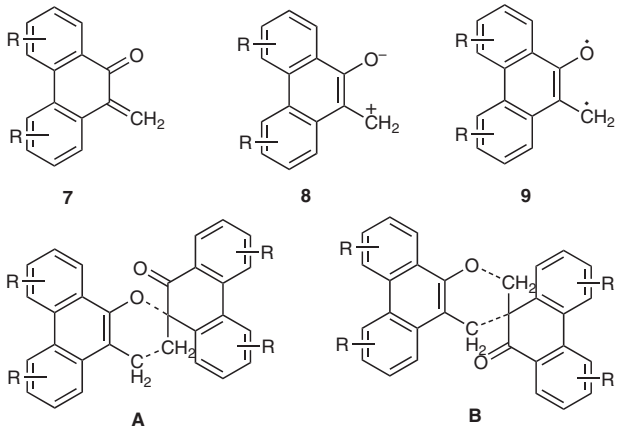
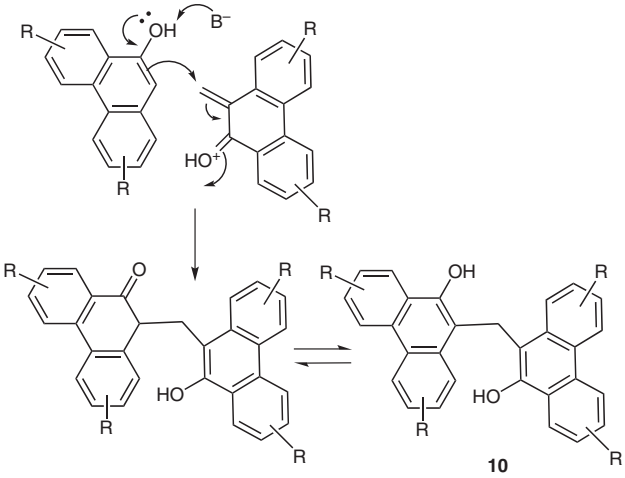


Figure 2



Scheme 4 Michael addition of 9-phenanthrol to10-methylene-9-phenanthrone

In conclusion, using proline as a recoverable catalyst, we have conveniently synthesized a new class of spirophenanthrones from 9-phenanthrols. Further biological activity testing of these compounds is in progress.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(9) **Synthesis of the Dimer of 10-Methylene-9-phenanthrones 1a–g – General Procedure**
To a stirred suspension of the 9-phenanthrol (1 mmol) in MeOH (10mL, **9d** was in THF–MeOH = 4:1), L-proline (6 mg, 0.05 mmol) and 36% aq formaldehyde (0.1 mL, 1.2 mmol) were added. The mixture was stirred at r.t. for 2–4 h. The reaction product was evaporated under vacuum. The residue was purified by flash column chromatography on SiO_2, eluting with PE–EtOAc, to produce the dimer of 10-methylene-9-phenanthrones.

(10) **Selective Spectroscopic Data of the Dimer of 10-Methylene-9-phenanthrones**
Compound **1a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.29 (m, 1 H), 2.54–2.60 (m, 2 H), 2.92 (m, 1 H), 3.72 (s, 3 H), 3.74 (s, 3 H), 3.77 (s, 3 H), 3.87 (s, 3 H), 3.89 (s, 3 H), 3.91 (s, 3 H), 3.96 (s, 6 H), 4.00 (s, 3 H), 4.02 (s, 3 H), 4.03 (s, 3 H), 4.06 (s, 3 H), 6.83 (s, 1 H), 7.11 (s, 1 H), 7.26 (s, 1 H), 7.68 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.6, 32.8, 55.9, 55.9, 56.1, 56.3, 61.0, 61.1, 61.1, 61.2, 61.2, 61.3, 61.4, 61.5, 83.1, 97.4, 98.0, 103.6, 105.2, 107.7, 113.1, 116.3, 117.7, 121.5, 123.1, 124.9, 132.4, 140.3, 142.3, 142.5, 146.7, 151.7, 151.8, 152.0, 152.2, 152.3, 152.4, 153.2, 153.6, 197.6. HRMS–FAB: *m/z* [M + H]$^+$ calcd for $C_{42}H_{44}O_{14}$: 773.2809; found: 773.2810. Anal. Calcd for $C_{42}H_{44}O_{14}$: C, 65.28; H, 5.74; O, 28.98. Found: C, 65.41; H, 5.72; O, 28.92.
Compound **1b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.27 (m, 1 H), 2.51 (m, 1 H), 2.82 (m, 1 H), 3.04 (m, 1 H), 3.83 (s, 3 H), 3.93 (s, 3 H), 3.96 (s, 3 H), 3.99 (s, 3 H), 4.00 (s, 3 H), 4.04 (s, 3 H), 4.10 (s, 3 H), 4.11 (s, 3 H), 4.14 (s, 3 H), 7.14 (s, 1 H), 7.24 (s, 1 H), 7.29 (s, 1 H), 7.36 (s, 1 H), 7.42 (s, 1 H), 7.52 (s, 1 H), 7.83 (m, 3 H). ^{13}C NMR (75 MHz, CDC_{l3}): δ = 19.6, 34.1, 55.8, 55.8, 56.0, 56.1, 56.2, 56.2, 56.3, 56.5, 82.3, 102.5, 103.1, 103.3, 103.9, 104.7, 106.9, 107.4, 108.7, 109.2, 119.7, 119.9, 121.5, 122.5, 124.6, 126.1, 131.6, 133.8, 146.6, 147.1, 148.7, 148.9, 149.0, 149.1, 149.2, 149.9, 154.5, 198.1. HRMS–FAB: *m/z* [M + H]$^+$ calcd for $C_{38}H_{36}O_{10}$: 653.2387; found: 653.2389. Anal. Calcd for $C_{38}H_{36}O_{10}$: C, 69.93; H, 5.56; O, 24.51. Found: C, 69.77; H, 5.50; O, 24.60.
Compound **1c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.27 (m, 1 H), 2.54 (m, 1 H), 2.60 (m, 1 H), 2.91 (m, 1 H), 3.89 (s, 3 H), 3.94 (s, 3 H), 3.99 (s, 3 H), 4.02 (s, 3 H), 6.03 (d, 2 H), 6.14

(d, 2 H), 6.17 (d, 2 H), 6.21 (d, 2 H), 6.80 (s, 1 H), 7.12 (s, 1 H), 7.17 (s, 1 H), 7.70 (s, 1 H). ^{13}C NMR (75 MHz, CDC_{13}): δ = 20.9, 33.9, 56.2, 56.3, 56.6, 56.7, 83.3, 97.4, 98.0, 101.2, 101.3, 101.8, 102.4, 102.8, 103.8, 106.1, 108.1, 115.1, 116.2, 117.9, 122.1, 123.4, 125.2, 132.6, 141.3, 142.3, 142.6, 145.0, 151.6, 151.8, 152.0, 152.2, 152.4, 152.5, 153.6, 154.2, 197.0. HRMS–FAB: *m/z* [M + H]$^+$ calcd for $C_{38}H_{28}O_{14}$: 709.1557; found: 709.1554. Anal. Calcd for $C_{38}H_{28}O_{14}$: C, 64.41; H, 3.98; O, 31.61. Found: C, 64.19; H, 3.41; O, 31.55.

Compound **1d**: ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.24 (m, 1 H), 2.33 (m, 1 H), 2.68 (m, 1 H), 3.42 (m, 1 H), 5.92 (s, 1 H), 6.06 (s, 2 H), 6.08 (s, 1 H), 6.09 (s, 1 H), 6.10 (s, 1 H), 6.19 (s, 1 H), 6.24 (s, 1 H), 7.02 (d, 1 H), 7.12 (d, 1 H), 7.26 (d, 1 H), 7.28 (d, 1 H), 7.55 (d, 1 H), 7.58 (d, 1 H), 8.16 (s, 1 H), 8.19 (s, 1 H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 20.0, 28.9, 80.2, 100.6, 101.1, 101.6, 108.8, 109.4, 111.8, 113.8, 116.4, 117.1, 117.4, 118.1, 120.0, 122.1, 124.1, 126.2, 129.7, 141.9, 144.9, 145.3, 145.7, 146.6, 147.9, 148.2, 193.7. HRMS–FAB: *m/z* [M + H]$^+$ calcd for $C_{34}H_{20}O_{10}$: 589.1135; found: 589.1136. Anal. Calcd for $C_{34}H_{20}O_{10}$: C, 69.39; H, 3.43; O, 27.19. Found: C, 69.54; H, 3.52; O, 27.05.

Compound **1e**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.22 (m, 1 H), 2.46 (s, 3 H), 2.49 (m, 1 H), 2.52 (s, 3 H), 2.58 (s, 3 H), 2.63 (s, 3 H), 2.76 (m, 1 H), 3.01 (m, 1 H), 7.22 (m, 2 H), 7.38 (d, 1 H), 7.45 (d, 1 H), 7.65–7.83 (m, 5 H), 8.38 (m, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.3, 21.4, 22.1, 22.2, 22.3, 34.0, 83.2, 108.5, 122.2, 122.4, 122.8, 123.6, 124.0, 125.0, 126.0, 126.3, 126.8, 127.9, 128.1, 128.3, 129.4, 129.9, 130.1, 133.0, 136.0, 136.8, 137.2, 137.7, 138.2, 145.3, 198.1. HRMS–FAB: *m/z* [M + H]$^+$ calcd for $C_{34}H_{28}O_2$: 469.2168; found: 469.2165. Anal. Calcd for $C_{34}H_{28}O_2$: C, 87.15; H, 6.02; O, 6.83. Found: C, 87.06; H, 5.98; O, 6.79.

Compound **1f**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.28 (td, 1 H), 2.55 (d, 1 H), 2.80 (td, 1 H), 3.09 (d, 1 H), 7.25–7.89 (m, 13 H), 8.52 (d, 1 H), 8.68 (t, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.5, 33.8, 83.2, 108.5, 122.4, 122.5, 123.0, 123.3, 124.0, 124.6, 126.0, 126.7, 128.8, 129.6, 130.1, 130.7, 132.0, 134.8, 136.9, 140.1, 148.0, 198.6. HRMS–FAB: *m/z* [M + H]$^+$ calcd for $C_{30}H_{20}O_2$: 413.1542; found: 413.1544. Anal. Calcd for $C_{30}H_{20}O_2$: C, 87.36; H, 4.89; O, 7.76. Found: C, 86.92; H, 4.88; O, 7.73.

Compound **1g**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.26 (m, 1 H), 2.50 (m, 1 H), 2.76 (m, 1 H), 3.01 (m, 1 H), 7.17 (m, 2 H), 7.37 (m, 2 H), 7.55 (m, 2 H), 7.74–7.85 (m, 2 H), 7.97 (m, 1 H), 8.15 (m, 2 H), 8.44 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.4, 33.9, 82.6, 102.2, 107.4, 107.9, 108.3, 108.6, 110.3, 110.6, 110.7, 111.5, 111.8, 115.8, 116.0, 116.2, 116.4, 116.7, 117.1, 117.4, 124.5, 124.6, 125.0, 125.1, 128.2, 128.3, 131.0, 131.1, 196.3. HRMS–FAB: *m/z* [M + H]$^+$ calcd for $C_{30}H_{16}F_4O_2$: 485.1165; found: 485.1169. Anal. Calcd for $C_{30}H_{16}F_4O_2$: C, 74.38; H, 3.33; F, 15.69; O, 6.61. Found: C, 74.55; H, 3.39; F, 15.58; O, 6.66.