

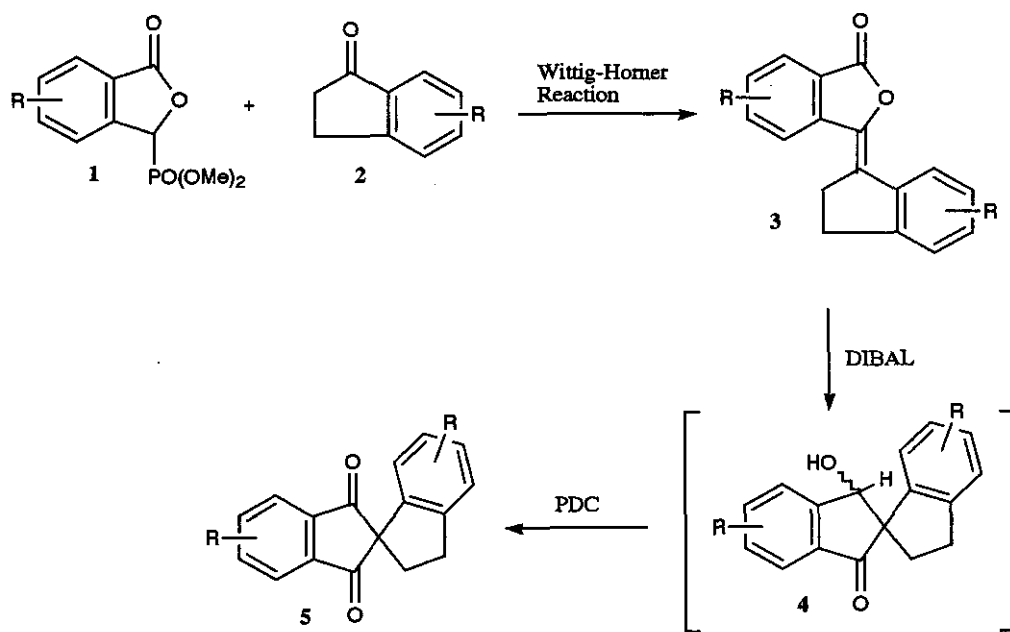
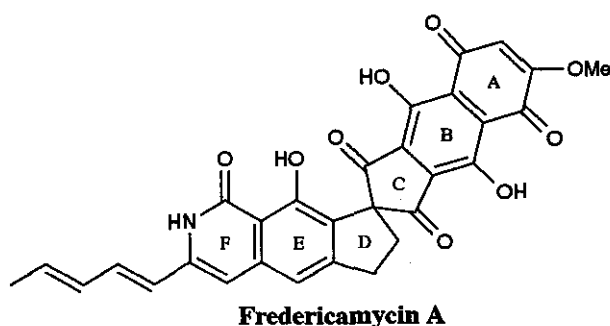
**SYNTHESIS OF 3-(1'-INDANYLIDENE)PHTHALIDES VIA WITTIG-HORNER REACTION OF DIMETHYL PHTHALIDE-3-PHOSPHONATES AND THEIR CONVERSION TO THE BCDE RING PART OF FREDERICAMYCIN A**

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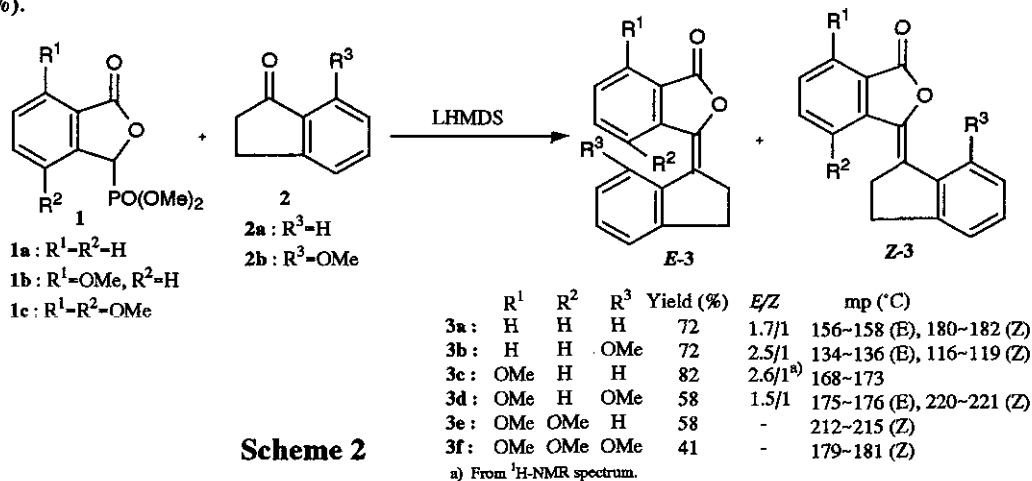
**Abstract-** Wittig-Horner reaction of dimethyl phthalide-3-phosphonates with 1-indanones in the presence of bases was investigated. The 3-(1'-indanylidene)phthalides obtained above were transformed into dibenzo-1,4-diketospiro[4.4]nonanes, the BCDE ring system of fredericamycin A, by consecutive treatments with diisobutylaluminum hydride and pyridinium dichromate.

Fredericamycin A, isolated from *Streptomyces griseus*, has been an attractive synthetic target because of its unique structural complexity and potent antitumour activity.<sup>1</sup> Many synthetic efforts including three total syntheses,<sup>2</sup> have focussed on the creation of the dibenzo-1,4-diketospiro[4.4]nonane system, the core of fredericamycin A, or its closely related derivatives. Major synthetic approaches to the spirocyclic system include a) radical spirocyclization,<sup>2b,2c,3</sup> b) Diels-Alder reaction,<sup>4</sup> c) Friedel-Crafts reaction,<sup>5</sup> d) spiro alkylation,<sup>6</sup> e) mercury-mediated acyl migration,<sup>7</sup> f) palladium-promoted intramolecular arylation,<sup>8</sup> g) photochemical cyclization,<sup>9</sup> h) intramolecular alkyne-chromium carbene benzannulation,<sup>10</sup> and i) transformation of ylidene-phthalides.<sup>2a</sup> As an application of phthalide-3-phosphonates<sup>11</sup> in organic synthesis,<sup>12</sup> we wish to report here a convenient synthesis of 3-(1'-indanylidene)phthalides (3) by Wittig-Horner reaction of dimethyl phthalide-3-phosphonates (1) with 1-indanones (2), and thereby establish a new general route to dibenzo-1,4-diketospiro[4.4]nonanes (5) as shown in Scheme 1.

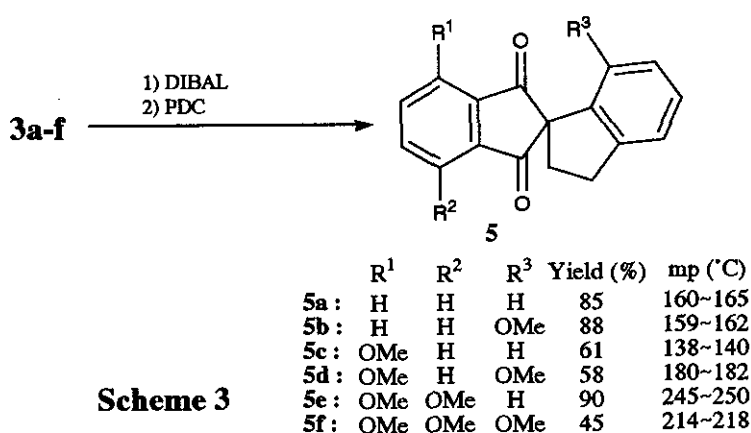


Dimethyl phthalide-3-phosphonate (**1a**)<sup>11</sup> was treated with 1.1 equivalent of lithium bis(trimethylsilyl)amide (LHMDS) in THF at  $-78^{\circ}\text{C}$  for 1 hour and then allowed to react with 1-indanone (**2a**) at room temperature for 10 hours under an argon atmosphere. After usual work-up, 3-(1'-indanylidene)phthalide (**3a**)<sup>13</sup> was obtained in 72% yield as a mixture of *E*- and *Z*-isomers in a 1.7/1 ratio.<sup>14</sup> If necessary, this mixture could be separated into *E*-**3a** and *Z*-**3a** by silica-gel column chromatography. When methoxy-substituted starting materials (**1b**, **c**, and **2b**) were employed in a similar Wittig-Horner reaction, a variety of methoxy-substituted indanylidene-phthalides (**3b-f**) was easily synthesized in modest to high yields as shown in Scheme 2. Although, despite several attempts, **3c** could not be separated into its *E*- and *Z*-isomers, the Wittig-Horner reactions of

**1a,b** with **2a,b** under the conditions described here predominantly provided *E*-isomers.<sup>12a</sup> However, in the reactions of **1c** with **2a** and **2b** (1.5 eq. LHMDS / -78°C / 3 h for generation of the anion of **1c**), only the *Z*-isomers of **3e** and **3f** were isolated in 58% and 41% yields, respectively. These results may be rationalized by considering the steric hindrance of the methoxy-substituent of **R**<sup>2</sup>. Sodium hydride (THF / 0°C to room temperature / 12 h) or cesium carbonate<sup>15</sup> (*i*-PrOH / room temperature / 24 h) can be used as bases in the reaction of **1a** with **2a**, and **3a** was obtained in 69% and 81% yields, respectively. These conditions seem to be equal or better than those using LHMDS, except for the reactions with the methoxy-substituted materials such as **1b** with **2b**, where the yields of **3d** decreased (40%: NaH; 23%: Cs<sub>2</sub>CO<sub>3</sub>) compared with that for LHMDS (58%).



Scheme 2



Scheme 3

Transformation of **3** synthesized here to spirocyclic **5** was achieved by the following sequences;<sup>2a, 16</sup> treatment of an *E/Z* mixture of **3a** with diisobutylaluminum hydride (DIBAL) in CH<sub>2</sub>Cl<sub>2</sub> at -78°C for 30 minutes

followed by the addition of a catalytic amount of sodium methoxide and then stirring at room temperature for 3 hours gave the spiroketo-alcohol (4a).<sup>2a</sup> This alcohol was oxidized with pyridinium dichromate (PDC) in  $\text{CH}_2\text{Cl}_2$  at room temperature for 12 hours to furnish desired 5a, 2a, 3a, 3c, 5, 7, 8a, 9a in 85% overall yield. Similarly, all methoxy-substituted indanylidene-phthalides (3b-f) were converted into the corresponding methoxy-substituted spirodiketones (5b-f)<sup>17</sup> in moderate to good overall yields as shown in Scheme 3.

In summary, we have developed a general and efficient route applicable to the regioselective preparation of methoxy-substituted dibenzo-1,4-diketospiro[4.4]nonane derivatives. Since it is based on the easy availability of methoxy-substituted dimethyl phthalide-3-phosphonates<sup>11</sup> and 1-indanones, this short route to spirocyclic diketones constitutes one of the most efficient syntheses of a model system for fredericamycin A reported to date.

#### ACKNOWLEDGMENT

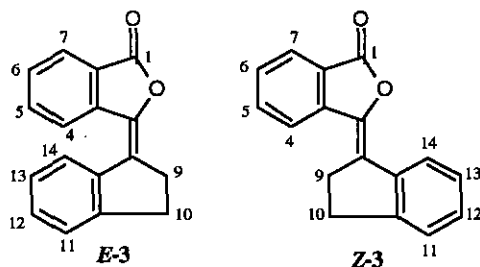
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13. This compound has been prepared using three steps (acylation of indene anion with dimethyl phthalate, lactonization with *p*-TsOH, and reduction with Raney Ni) as a model study in the total synthesis of fredericamycin A by Kelly *et al.*,<sup>2a</sup> and , furthermore, photochemical reaction of indene with 3,3-dichlorophthalide by Naik *et al.*<sup>9b</sup>
14. The stereochemistry of *E*- and *Z*-isomers was determined using their nuclear Overhauser effect (NOE) experiments. For example, the irradiation of C-4 proton ( $\delta$  8.32, d,  $J=8.1$  Hz) of *E*-3a produced NOE enhancement at the signals of C-5 ( $\delta$  7.71, ddd,  $J=1.1, 7.7, 8.1$  Hz) and C-14 ( $\delta$  8.00-8.03, m). In the case of *Z*-3a, the irradiation of C-4 proton ( $\delta$  7.71-7.73, m with C-5 proton) produced NOE enhancement at the signal of C-9 ( $\delta$  3.19-3.23, m), but no NOE enhancement at C-14 proton ( $\delta$  8.30-8.32, m) was observed. Furthermore, the irradiations of methoxy protons of *E*-3b ( $\delta$  3.85, s) and *Z*-3b ( $\delta$  4.01, s) produced NOE enhancements at the signals of C-4 ( $\delta$  7.43, dd,  $J=0.7, 8.1$  Hz) and C-13 ( $\delta$  6.86, d,  $J=8.4$  Hz) protons, and C-13 proton ( $\delta$  6.84, d,  $J=8.1$  Hz), respectively. Typical <sup>1</sup>H- (400 MHz) and <sup>13</sup>C-nmr data (100 MHz): *E*-3b;  $\delta$  7.91 (1H, dd,  $J=1.1, 7.7$  Hz, H-7), 7.62 (1H, ddd,  $J=1.1, 7.7, 8.1$  Hz, H-5), 7.45 (1H, dd,  $J=0.7, 8.1$

Hz, H-6), 7.43 (1H, dd,  $J=0.7, 8.1$  Hz, H-4), 7.33 (1H, t,  $J=7.7$  Hz, H-12), 7.00 (1H, dd,  $J=0.7, 7.3$  Hz, H-11), 6.86 (1H, d,  $J=8.4$  Hz, H-13), 3.85 (3H, s, MeO), 3.24-3.27 (2H, m, H-9), 3.02-3.05 (2H, m, H-10);  $\delta$  31.80, 34.87, 54.61, 109.06, 117.66, 124.66, 125.48, 125.79, 126.61, 128.13, 130.81, 132.80, 138.56, 140.35, 151.64, 155.06, 167.48. **Z-3b**;  $\delta$  7.97 (1H, dd,  $J=1.1, 7.7$  Hz, H-7), 7.79 (1H, d,  $J=8.1$  Hz, H-4), 7.70 (1H, ddd,  $J=1.1, 7.7, 8.1$  Hz, H-5), 7.49 (1H, dd,  $J=0.7, 7.7$  Hz, H-6), 7.30 (1H, t,  $J=7.3$  Hz, H-12), 6.93 (1H, dd,  $J=0.7, 7.3$  Hz, H-11), 6.84 (1H, d,  $J=8.1$  Hz, H-13), 4.01 (3H, s, MeO), 3.23-3.27 (2H, m, H-9), 3.13-3.16 (2H, m, H-10);  $\delta$  31.45, 31.60, 56.01, 110.46, 117.15, 122.83, 125.09, 125.25, 125.68, 127.19, 128.40, 131.28, 133.93, 137.86, 140.27, 149.42, 156.77, 167.24. **5b**;  $\delta$  8.00-8.03 (2H, m), 7.85-7.89 (2H, m), 7.22 (1H, t,  $J=7.7$  Hz), 6.93 (1H, dd,  $J=0.7, 7.3$  Hz), 6.56 (1H, d,  $J=8.1$  Hz), 3.40 (3H, s), 3.27 (2H, t,  $J=7.3$  Hz), 2.46 (2H, t,  $J=7.3$  Hz);  $\delta$  32.58, 34.95, 55.19, 64.73, 108.51, 117.46, 123.18, 130.31, 135.37, 141.75, 148.37, 155.06, 202.82.



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17. In the methoxy-substituted debenzo-1,4-diketospiro[4.4]nonanes prepared here, **5b<sup>3c</sup>**, **5e<sup>5a</sup>** and **5f<sup>3d</sup>** has been synthesized.

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