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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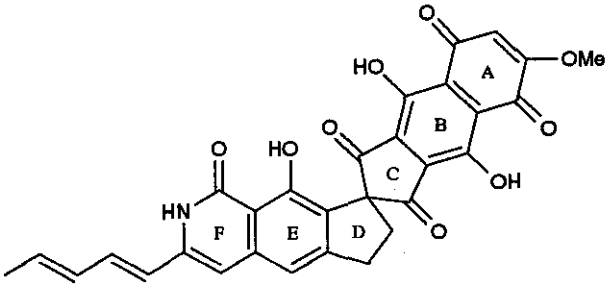
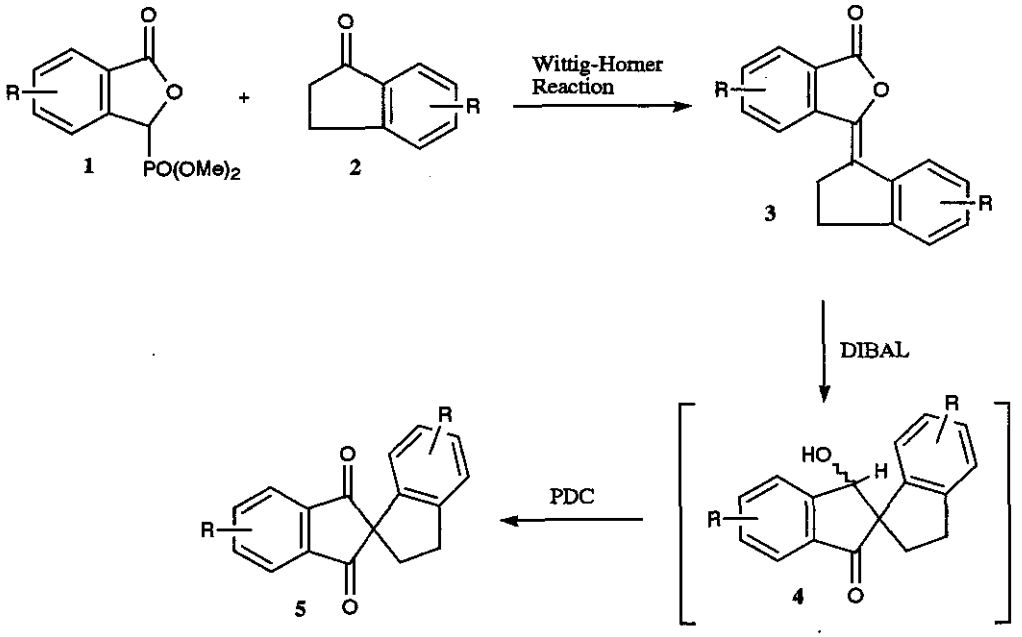
Abstract- Wittig-Horner reaction of dimethyl phthalide-3-phosphonates with 1-indanones in the presence of bases was investigated. The 3-(1′-indanylidene)phthalides obtained above were transformed into dibenzo-1,4-diketospiro[4.4]nonanes, the BCDE ring system of fredericamycin A, by consecutive treatments 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.[1] Many synthetic efforts including three total syntheses,[2] 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,[2b,2c,3] b) Diels-Alder reaction,[4] c) Friedel-Crafts reaction,[5] d) spiro alkylation,[6] e) mercury-mediated acyl migration,[7] f) palladium-promoted intramolecular arylation,[8] g) photochemical cyclization,[9] h) intramolecular alkyne-chromium carbene benzannulation,[10] and i) transformation of ylidenephthalides.[2a] As an application of phthalide-3-phosphonates[11] in organic synthesis,[12] 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**.



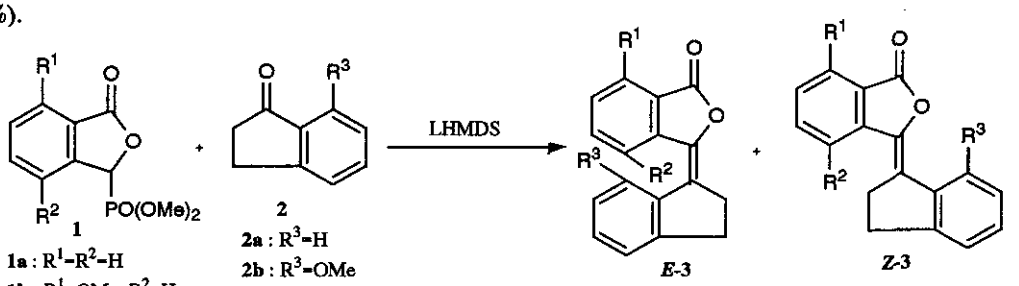
Fredericamycin A



Scheme 1

Dimethyl phthalide-3-phosphonate (**1a**)[11] was treated with 1.1 equivalent of lithium bis(trimethylsilyl)amide (LHMDS) in THF at -78°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**)[13] was obtained in 72% yield as a mixture of *E*- and *Z*-isomers in a 1.7/1 ratio.[14] If neccessary, 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 indanylidenephthalides (**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.[12a] 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^2. Sodium hydride (THF / 0°C to room temperature / 12 h) or cesium carbonate[15] (*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_2CO_3) compared with that for LHMDS (58%).



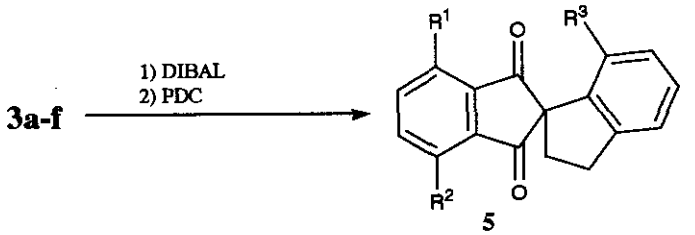
1a : R^1=R^2=H
1b : R^1=OMe, R^2=H
1c : R^1=R^2=OMe

2a : R^3=H
2b : R^3=OMe

Scheme 2

	R^1	R^2	R^3	Yield (%)	*E/Z*	mp (°C)
3a :	H	H	H	72	1.7/1	156~158 (E), 180~182 (Z)
3b :	H	H	OMe	72	2.5/1	134~136 (E), 116~119 (Z)
3c :	OMe	H	H	82	2.6/1[a)]	168~173
3d :	OMe	H	OMe	58	1.5/1	175~176 (E), 220~221 (Z)
3e :	OMe	OMe	H	58	-	212~215 (Z)
3f :	OMe	OMe	OMe	41	-	179~181 (Z)

a) From ^{1}H-NMR spectrum.



Scheme 3

	R^1	R^2	R^3	Yield (%)	mp (°C)
5a :	H	H	H	85	160~165
5b :	H	H	OMe	88	159~162
5c :	OMe	H	H	61	138~140
5d :	OMe	H	OMe	58	180~182
5e :	OMe	OMe	H	90	245~250
5f :	OMe	OMe	OMe	45	214~218

Transformation of **3** synthesized here to spirocyclic **5** was achieved by the following sequences;[2a, 16] treatment of an *E/Z* mixture of **3a** with diisobutylaluminum hydride (DIBAL) in CH_2Cl_2 at -78°C for 30 minutes

followed by the addition of a catalytic amount of sodium methoxide and then stirring at room temparature for 3 hours gave the spiroketo-alcohol (**4a**).[2a] This alcohol was oxidized with pyridinium dichromate (PDC) in CH_2Cl_2 at room temperature for 12 hours to furnish desired **5a**[2a], 3a, 3e, 5, 7, 8a, 9a in 85% overall yield. Similarly, all methoxy-substituted indanylidenephthalides (**3b-f**) were converted into the corresponding methoxy-substituted spirodiketones (**5b-f**)[17] 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[11] 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.

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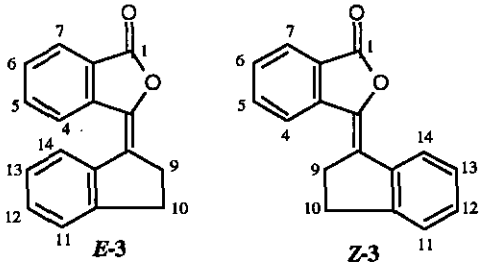
13. This compound has been prepared using three steps (acylation of indene anion with dimethyl phthalate, lactonization with *p*-TsOH, and reduction with Raney Ni) as a model study in the total synthesis of fredericamycin A by Kelly *et al.*,[2a] and , furthermore, photochemical reaction of indene with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



E-3 *Z*-3

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

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