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. Many synthetic efforts including three total syntheses, 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, b) Diels-Alder reaction, c) Friedel-Crafts reaction, d) spiro alkylation, e) mercury-mediated acyl migration, f) palladium-promoted intramolecular arylation, g) photochemical cyclization, h) intramolecular alkyne-chromium carbene benzannulation, and i) transformation of ylidenephthalides. As an application of phthalide-3-phosphonates in organic synthesis, 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)\(^{11}\) 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 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 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. 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 R2. Sodium hydride (THF / 0°C to room temperature / 12 h) or cesium carbonate (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%: Cs2CO3) compared with that for LHMDS (58%).

Transformation of 3 synthesized here to spirocyclic 5 was achieved by the following sequences: treatment of an E/Z mixture of 3a with diisobutylaluminum hydride (DIBAL) in CH2Cl2 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 spirokebalcohol (4a).2a This alcohol was oxidized with pyridinium dichromate (PDC) in CH₂Cl₂ at room temperature for 12 hours to furnish desired 5a, 3a, 3c, 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) 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 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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REFERENCES AND NOTES


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., and, furthermore, photochemical reaction of indene with 3,3-dichlorophthalide by Naik et al.

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 1H- (400 MHz) and 13C-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.

17. In the methoxy-substituted debenzo-1,4-diketospiro[4.4]nonanes prepared here, 5b3c, 5e5a and 5f3d has been synthesized.

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