Oxidative Intramolecular [4 + 2]Cycloaddition of Silylene-protected 2-Pyridone Derivatives—A Short and Efficient Synthesis of the *DEF*-Ring of Fredericamycin A

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Thermal treatment of 2-pyridone derivatives **2** with dimethyldichlorosilane, triethylamine and chloranil in benzene gives 8-hydroxyisoquinolones **4** in high yields by oxidative intramolecular [4 + 2]cycloaddition which are used in the synthesis of the fully functionalized *DEF*-ring **14** of fredericamycin A.

The development of an efficient synthesis of biologically important naturally occurring *peri*-hydroxy aromatic compounds,¹ such as anthracyclines, pyranonaphthoquinones, fredericamycin A and other antitumour polycyclic aromatic antibiotics, has been the subject of intense study. In connection with our efforts² towards the synthesis of these types of compounds, we have reported the novel oxidative [4 + 2] cycloaddition of silylene-protected *o*-hydroxyphenyl ketone to dienophiles³ and have extended it to the intramolecular system.⁴ If this silylene-protected cycloaddition reaction can be applied to a 2-pyridone system instead of the *o*-hydroxyphenyl system, it could be quite useful for the synthesis of biologically important 8-hydroxyisoquinolone compounds, such as strongly cytotoxic fredericamycin A 1⁵ and actinoplan-





Actinoplanone A X = O, Y = C=O, R¹ = CI, R² = Me, R³ = OH, R⁴ = β -OMe

Ibofungin
$$X = C = O$$
, $Y = O$, $R^1 = R^2 = R^3 = H$, $R^4 = \alpha$ -OMe

Fig 1 Antibiotics including 8-hydroxyisoquinolone frameworks



one A^6 and active antibacteria albofungin⁷ (Fig. 1). We report here an effective oxidative intramolecular [4 + 2]cycloaddition reaction of silylene-protected 3-acyl-2-pyridone derivatives 2 having a suitable dienophile in the side chain and application to a short and efficient synthesis of the fully functionalized *DEF*-ring 14 of fredericamycin A 1.

The starting 3-acyl-2-pyridones 2a-c were prepared from 3acetyl-2-pyridone 58 in 6 steps via 3-acryloyl-2-methoxypyridine as in the synthesis of N-[3-(2-hydroxyphenyl)-3oxopropyl]-N-phenylpropiolamides from 3-anilino-1-(2-hydroxyphenyl)-1-propanone.⁴ Initially, heating of a benzene solution of 2-pyridone 2a having a (phenylethynyl)amido side chain, dimethyldichlorosilane (4 equiv.) and triethylamine (8 equiv.) at refluxing temperature for 3 h gave a low yield (16%) of the cycloadduct, 8-hydroxyisoquinolone 4a along with recovered 2a in a 63% yield. The latter is probably due to the regeneration of 2a from the initially formed bis(2-pyridon-1yl)dimethylsilane.9 When the reaction was performed in the presence of chloranil (2.5 equiv.) at a higher temperature (90-100°C) in a sealed tube, the yield of 4a was dramatically improved (87%). Similar treatment of 2b-d provided the corresponding cycloadducts 4b-d in high yields (Table 1). The structures of the products 4a-d were confirmed by spectroscopic data and microanalyses. In these reactions, the conjugated double bonds of the in situ generated O,O-silvlene derivatives **3** acted as active 4π -components giving high yields of the cycloadducts 4.

We applied this cycloaddition to the short and efficient synthesis of the fully functionalized *DEF* ring 14 of fredericamycin A 1. In order to construct the *DEF*-ring system of 1, the choice of the terminal substituent R of the dienophile, which is converted to hydrogen after the ring formation, is crucial. Treatment of the unsubstituted 2-pyridone 10, prepared from 5 in 5 steps, with dimethyldichlorosilane, triethylamine and chloranil in dry benzene at 150°C for 5 days in a

Table 1 Preparation of 8-hydroxyisoquinolones 4 from 2-pyridones 2



sealed tube gave the cycloadduct 11 in a 12% yield along with recovered 10 (67%). Treatment of the trimethylsilyl derivative 9 under similar conditions produced the desired protodesilylation adduct 11 in a 58% yield accompanied by recovered 9 (19%). The use of imidazole instead of triethylamine accelerated this reaction to give 11 in an 82% yield. Functionalization of the F-ring methyl group of 11 was attained very cleanly by SeO_2 -oxidation to give the aldehyde 12 in a 96% yield.[†] Wittig reaction of 12 with the phosphorus ylide generated from 13 gave 14 as a mixture of geometrical isomers of the diene, which was isomerized to (E), (E)-14 by treatment with a catalytic amount of iodine in a 71% yield.‡ All new compounds were fully characterized by spectroscopy and microanalysis.§ The fully functionalized DEF-ring was synthesized in only 8 steps with a 35% overall yield. which is an improvement on previously reported syntheses.¹⁰



Scheme 1 Reagents and conditions: (i) MeI, Ag₂CO₃, ultrasound, benzene, room temp., 20 h, 83%; (ii) Me₃SiOTf, Et₃N, CH₂Cl₂, -55° C, 30 min; then NBS, THF, -45° C, 30 min, 97%; (iii) 8, NaH, DMF, $-55 \rightarrow -^{\circ}$ C, 1 h, 86%; (iv) NaBr, *p*-TsOH, MeOH, reflux, 2 h, 89%; (v) NaOMe, MeOH, room temp., 1 d, 61%; (vi) Me₂SiCl₂ (4 equiv.), imidazole (8 equiv.), chloranil (2.5 equiv.), benzene, 180°C, 42 h, 82%; (vii) SeO₂, dioxane, reflux, 4 h, 96%; (viii) 13, BuⁿLi, THF, 0°C, 1 h; then 12, -75° C, 30 min \rightarrow room temp. 10 min; (ix) l₂ (*ca* 0.02 equiv.), CH₂Cl₂, room temp. 12 h, 71% from 12.

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Footnotes

[†] Other attempts to functionalize the methyl group of 11 by (a) bromination of 11 or (b) lithiation of 11 followed by quenching with heteroatom electrophiles resulted in complex mixtures.

‡ This product was contaminated with 8% (Z),(E)-14, from which ≥98% pure (E),(E)-14 was obtained by recrystallization from hexane-benzene. A prolonged reaction time was not effective.

§ Physical and spectral data for 11, 12 and (E),(E)-14 are as follows: 11, mp 294–298°C (hexane–CHCl₃); 12, mp 269–272°C (hexane–CHCl₃; *J* in Hz); (E),(E)-14, mp 218–220°C (decomp.) (hexane–benzene), v_{max} (KBr)/cm⁻¹ 1734, 1653 and 1614; $\delta_{\rm H}$ (500 MHz; 0.02 mol dm⁻³ in CDCl₃; *J* in Hz) 1.87 (3 H, d, *J* 6.5), 2.81 (2 H, t, *J* 7.5), 3.78 (6 H, s), 6.06 (1 H, dq, *J* 15.5 and 6.5), 6.13 (1 H, d, *J* 15.5), 6.18–6.23 (1 H, m), 6.38 (1 H, s), 6.77 (1 H, dd, *J* 15.5 and 10), 6.81 (1 H, s), 9.77 (1 H, br s) and 12.79 (1 H, s).

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