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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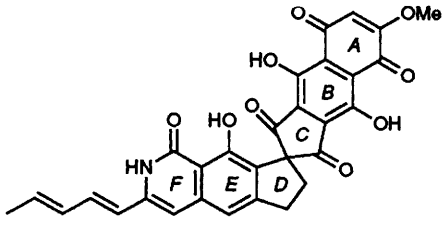
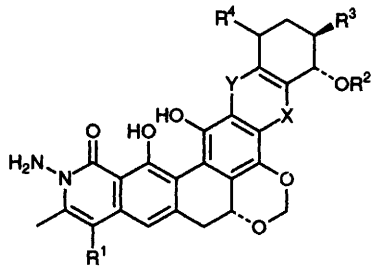
Thermal treatment of 2-pyridone derivatives **2** with dimethyldichlorosilane, triethylamine and chloranil in benzene gives 8-hydroxyisoquinolones **4** in high yields by oxidative intramolecular [4 + 2]cycloaddition which are used in the synthesis of the fully functionalized *DEF*-ring **14** of fredericamycin 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 efforts[2] towards the synthesis of these types of compounds, we have reported the novel oxidative [4 + 2] cycloaddition of silylene-protected *o*-hydroxyphenyl ketone to dienophiles[3] 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 **1**[5] and actinoplanone A[6] and active antibacteria albofungin[7] (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**.



Fredericamycin A

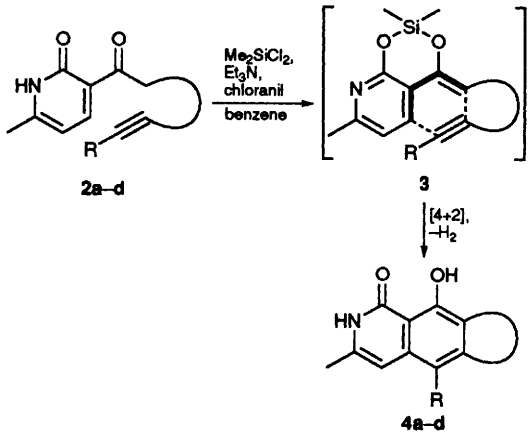
1



Actinoplanone A X = O, Y = C=O, R^1 = Cl, R^2 = Me, R^3 = OH, R^4 = β-OMe

Albofungin X = C=O, Y = O, R^1 = R^2 = R^3 = H, R^4 = α-OMe

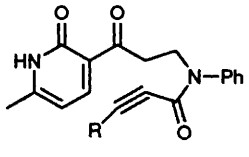
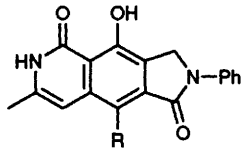
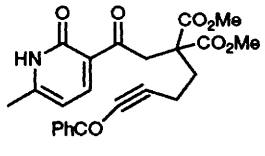
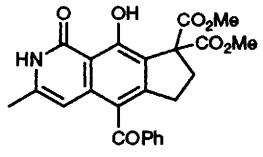
Fig 1 Antibiotics including 8-hydroxyisoquinolone frameworks



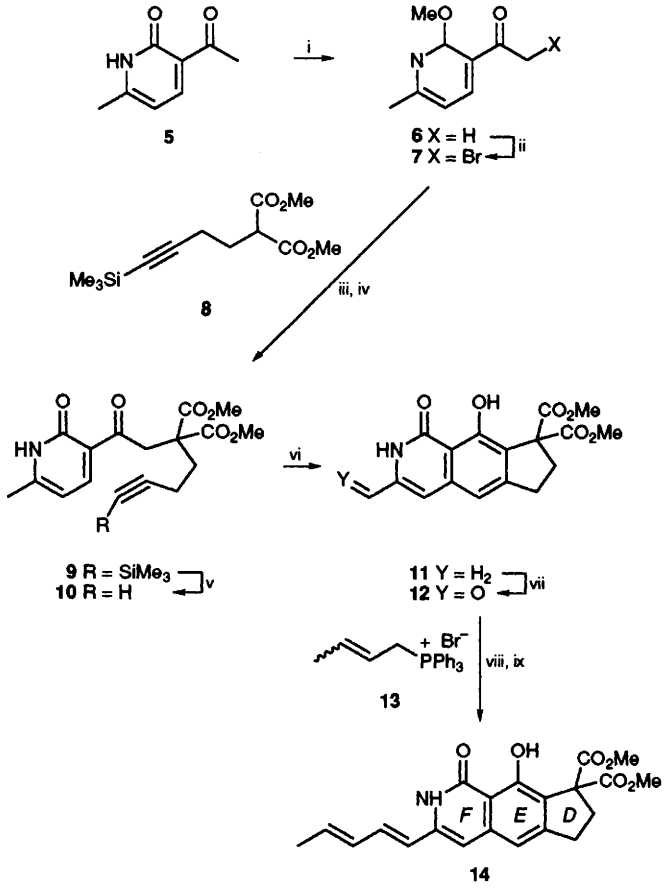
The starting 3-acyl-2-pyridones **2a–c** were prepared from 3-acetyl-2-pyridone **5**[8] in 6 steps *via* 3-acryloyl-2-methoxypyridine as in the synthesis of *N*-[3-(2-hydroxyphenyl)-3-oxopropyl]-*N*-phenylpropiolamides from 3-anilino-1-(2-hydroxyphenyl)-1-propanone.[4] Initially, heating of a benzene 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-1-yl)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*-silylene 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**

2-Pyridone **2**	Reaction conditions	8-Hydroxyisoquinolone **4** (yield)
		
2a R = Ph **b** R = Me **c** R = H	90°C, 3h 95°C, 9h 130°C, 20h	**4a** R = Ph (87%) **b** R = Me (99%) **c** R = H (98%)
		
2d	130°C, 5h	**4d** (74%)

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 proto-desilylation 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, Ag_2CO_3, ultrasound, benzene, room temp., 20 h, 83%; (ii) Me_3SiOTf, Et_3N, CH_2Cl_2, −55°C, 30 min; then NBS, THF, −45°C, 30 min, 97%; (iii) **8**, NaH, DMF, −55 → −°C, 1 h, 86%; (iv) NaBr, *p*-TsOH, MeOH, reflux, 2 h, 89%; (v) NaOMe, MeOH, room temp., 1 d, 61%; (vi) Me_2SiCl_2 (4 equiv.), imidazole (8 equiv.), chloranil (2.5 equiv.), benzene, 180°C, 42 h, 82%; (vii) SeO_2, dioxane, reflux, 4 h, 96%; (viii) **13**, Bu^nLi, THF, 0°C, 1 h; then **12**, −75°C, 30 min → room temp. 10 min; (ix) I_2 (*ca* 0.02 equiv.), CH_2Cl_2, 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–$CHCl_3$); **12**, mp 269–272°C (hexane–$CHCl_3$; *J* in Hz); (*E*),(*E*)-**14**, mp 218–220°C (decomp.) (hexane–benzene), ν_{max} (KBr)/cm^{-1} 1734, 1653 and 1614; δ_H (500 MHz; 0.02 mol dm^{-3} in $CDCl_3$; *J* in Hz) 1.87 (3 H, d, *J* 6.5), 2.81 (2 H, t, *J* 7.5), 3.03 (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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