Manganese(III) Mediated Synthesis of Spiro[4,4]Nonane System Present in Fredericamycin A†

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A convenient approach for constructing the spiro[4,4]nonane system of Fredericamycin A has been demonstrated using a manganese(III) based oxidative free radical cyclisation.

Fredericamycin A (**1**), an antitumour antibiotic produced by *Streptomyces griseus*,[1] has been the target of much synthetic interest not only owing to its biological activity but also because of its structural complexity.[2] We have reported the novel methodology for constructing the spiro system by thermal isomerisation[2a] and subsequently achieved the synthesis of the two main segments, *ABC* and *DEF*, desired for completing our goal.[3] Further progress in our attempts to

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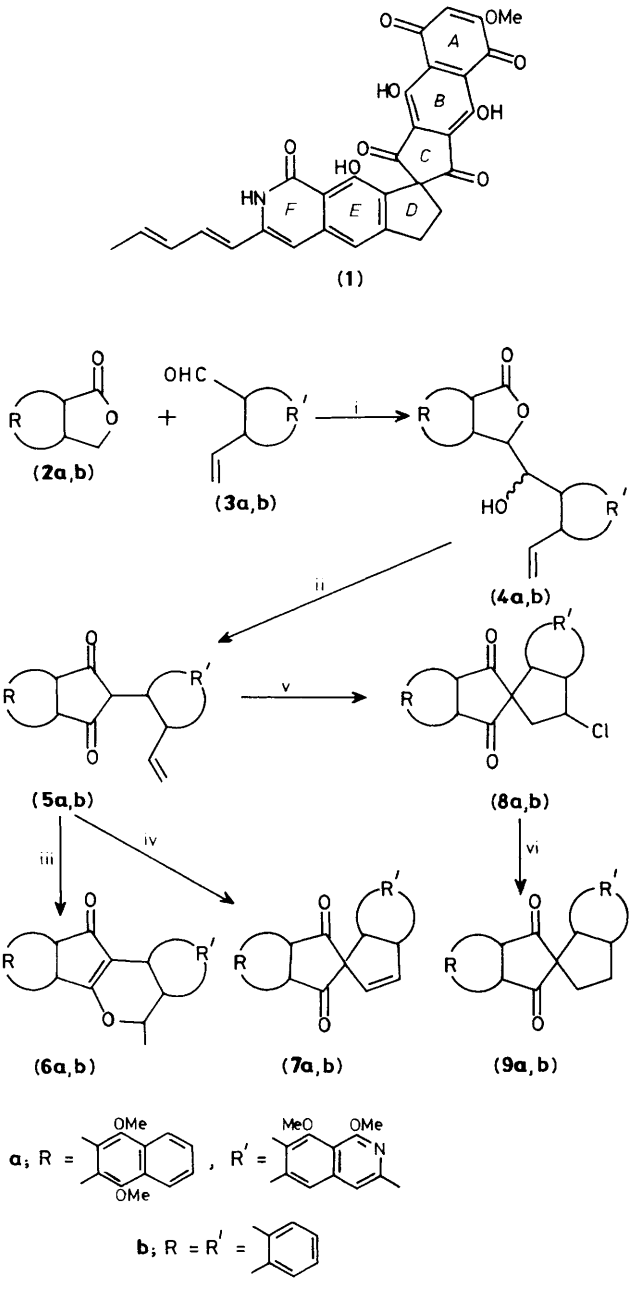

Scheme 1. *Reagents and conditions:* i, LDA, tetrahydrofuran (THF), hexamethylphosphoramide (HMPA), −78 °C, 20 min; ii, NaOMe, MeOH, ethyl propionate, reflux, 1.5 h; iii, Silica gel column, acetone–$CHCl_3$–Petroleum ether or cat. HCl/$CHCl_3$; iv, manganese(III) acetate (1 equiv.), copper(II) acetate (1 equiv.), acetic acid (0.1 M), room temp., 30 min; v, manganese(III) acetate (1 equiv.), copper(II) acetate (1 equiv.), $CHCl_3$ (1 equiv.), room temp., 30 min; vi, Pd–C/H_2, MeOH, room temp., 12 h.

complete the synthesis of (**1**) was hampered by the non-availability of appropriate synthetic technology which need much milder conditions. We now report a very mild and general approach for constructing the spiro[4,4]nonane system utilising manganese(III) based oxidative free radical cyclisation which was previously reported for the preparation of lactones[4a] and cyclic ketones[4b] as depicted in Scheme 1.

A typical procedure was as follows. Treatment of (**3a**)‡ with lithium diisopropylamide (LDA) and phthalide (**2a**)‡ gave the aldol adduct (**4a**) in good yield (80%) as a mixture of diastereoisomers which were not separated. Dieckmann cyclisation with sodium methoxide and ethyl propionate as a scavenger in methanol[5] on refluxing provided the 1,3-dione (**5a**) (93% yield), which cyclised to the spiro compound (**7a**) (72%) upon stirring for 30 min at room temperature with manganese(III) acetate (1 equiv.) and copper(II) acetate (1 equiv.) in acetic acid (0.1 M). However, in the presence of chloroform (1 equiv.) (**5a**) gave exclusively the chloro product (**8a**) (68%). On stirring (**5a**) with acid in chloroform (**6a**) was produced in 96% yield. Catalytic reduction of (**8a**) over palladium–carbon in methanol afforded (**9a**) (86% yield).§ The ^{1}H n.m.r. spectral signals of the methylene protons of (**9a**) coincided with the literature values for Fredericamycin A.

Compound (**9b**) was synthesised in the same way except for the 1,3-dione, which was obtained directly from the corresponding phthalide and aldehyde by refluxing with sodium methoxide in methanol[5]. The spectral data for (**9b**) (i.r., m.s., ^{1}H n.m.r.) were identical with those reported[2a] previously.

Acid catalysed[6] reaction of (**5a,b**) only provided the six membered cyclic enol ether (**6a,b**) instead of the spiro product. On the other hand, the formation of (**7a,b; 8a,b**) proceeds *via* an unusual radical 5-*endo* trigonal cyclisation.[7]

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‡ The synthesis of these compounds will be reported elsewhere.

§ All compounds reported have mass spectral and spectroscopic data in accordance with their structures.