Stereocontrolled Synthesis of 4-Demethoxy-7-*O*-methyldaunomycinone

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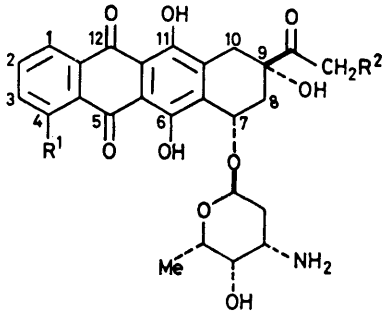
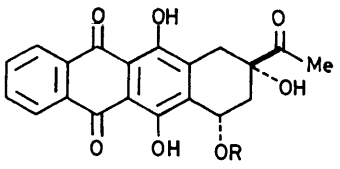
Summary The Diels–Alder adduct (**6**), prepared from 4a,9a-epoxy-4a,9a-dihydroanthracene-1,4,9,10-tetraone (**3**) and 1-methoxy-3-trimethylsilyloxybuta-1,3-diene, can be efficiently converted into the title compound (**2b**), a precursor of 4-demethoxydaunomycin (**1d**), by a five-step sequence.

DAUNOMYCIN (**1a**), adriamycin (**1b**), and carminomycin (**1c**), members of the anthracycline group of antibiotics, are of considerable interest because of their effectiveness against a range of human cancers. The clinical utility of these antibiotics is limited, however, by their dose-related cardiotoxicities.[1] In the hope of defining structure–activity–toxicity relationships, an intense effort is currently being devoted to the synthesis of structurally modified derivatives.[1,2] One of the most promising analogues to emerge from these studies is 4-demethoxydaunomycin (**1d**); besides being less cardiotoxic than daunomycin (**1a**), it is 8—10 times more active.[3] At present 4-demethoxydaunomycin (**1d**) is prepared, following deprotection, by coupling 4-demethoxydaunomycinone (**2a**), available only by total synthesis, with a protected form of L-daunosamine.[3]



(1)

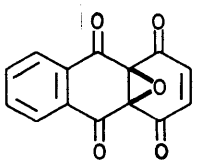
a; R^1 = OMe, R^2 = H
b; R^1 = OMe, R^2 = OH
c; R^1 = OH, R^2 = H
d; R^1 = R^2 = H



(2)

a; R = H
b; R = Me

Recently, we described[4] a simple synthesis of the oxiran (**3**) and showed that the compound readily underwent cycloaddition reactions with isoprene, cyclopentadiene, and cyclohexa-1,3-diene; we also reported that the derived cycloadducts, *e.g.* (**4**), could be converted into the quinizarins, *e.g.* (**5**). We now further illustrate the value of the



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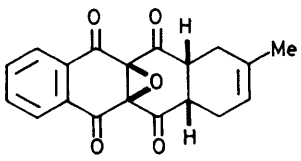
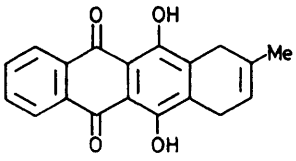


(4)



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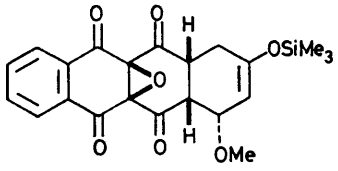

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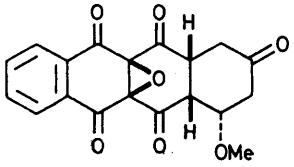

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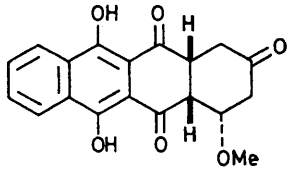

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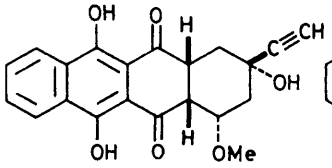

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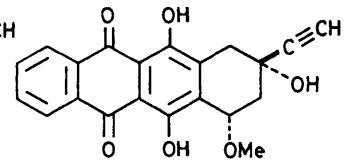

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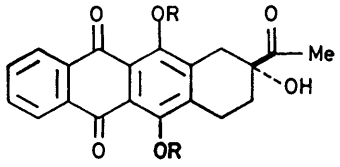

(11)

oxiran (**3**) by describing its conversion into 4-demethoxy-7-*O*-methyldaunomycinone (**2b**), a direct precursor[3] of 4-demethoxydaunomycinone (**2a**). Significantly, the six-step sequence requires no column purification step and proceeds in *ca.* 23% overall yield.

Treatment of the oxiran (**3**) with 1-methoxy-3-trimethylsilyloxybuta-1,3-diene (1·1 mol. equiv.) (CH_2Cl_2, 0 °C → room temp., in the dark) gave the light-sensitive cycloadduct (**6**)† (70%), m.p. 162—164 °C (decomp.), which was converted under acidic conditions [tetrahydrofuran–0·1M-HCl (30 : 1)][5] into the light-sensitive ketone (**7**)† (70%), m.p. 173—176 °C (decomp.). The bright-yellow leucoquinizarin (**8**)† (95%), m.p. 171—173 °C (decomp.), obtained from the ketone (**7**) by reduction with sodium dithionite (2·2 mol. equiv.) [MeOH–H_2O (4 : 1)],[4] afforded the acetylene (**9**)† (70%), m.p. 176—178 °C (decomp.), as yellow needles, when treated with ethynylmagnesium bromide (5 mol. equiv.) (tetrahydrofuran, 0 → 25 °C, NH_4Cl work-up).[6] In the presence of lead(IV) acetate (1·2 mol. equiv.) and acetic acid, the acetylene (**9**) was transformed into the quinizarin (**10**),† m.p. 228—236 °C (decomp.), isolated by filtration as shiny red plates in 73% yield. When heated with mercury(II) oxide (2·5 mol. equiv.) [Me_2CO–7% H_2SO_4 (2 : 1)], the quinizarin (**10**) gave the red 4-demethoxy-7-*O*-methyldaunomycinone (**2b**)‡ (95%), m.p. 230—234 °C (lit.[7] 250—254 °C).

4-Demethoxydaunomycinone (**2a**) has been synthesised on several previous occasions. In the majority of these routes,[2] a tetracycle of type (**11**) is assembled, which is subsequently functionalised at position 7. A key feature of the present approach is that the tetracycle is constructed with the oxygen functionality at position 7,§ a strategy that has been successfully executed on only two previous occasions.[5,8]

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† The composition of this compound, obtained as a racemate, was confirmed by elemental analysis and/or by high-resolution mass spectroscopy; its structure was corroborated by n.m.r., i.r., and u.v. spectroscopic evidence.

‡ Although this compound showed a m.p. significantly lower than that reported, its spectral properties were in agreement with those published.

§ The trimethylsilyl moiety has also been used as a precursor of oxygen functionality at position 7 (R. B. Garland, J. R. Palmer, J. A. Schulz, P. B. Sollman, and R. Pappo, *Tetrahedron Lett.*, 1978, 3669).

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