

A New Approach to Linear Tetracycles *via* Michael Reactions of Quinizarinquinone with *O*-Silylated Ketene Acetals

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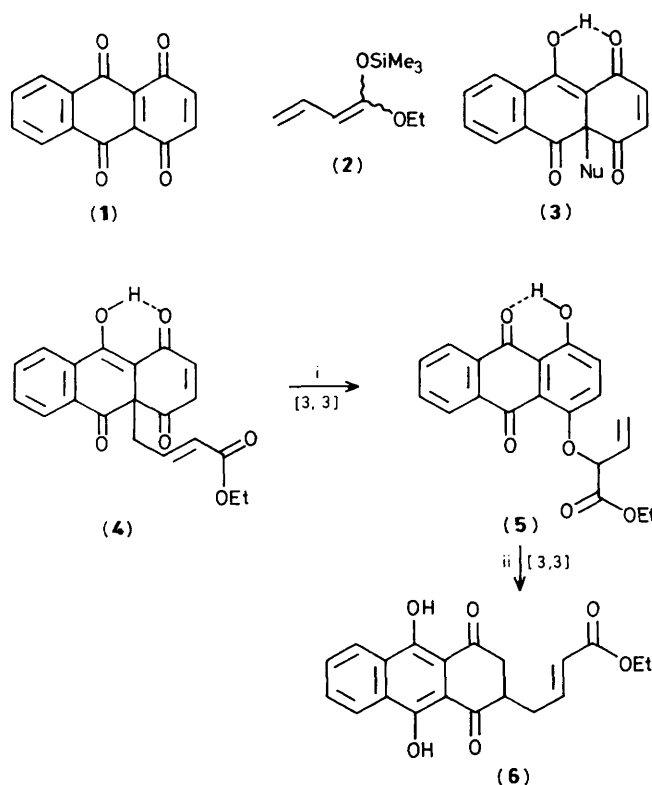
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The Michael-type reaction of quinizarinquinone and 1-ethoxy-1-(trimethylsiloxy)buta-1,3-diene followed by Lewis acid-catalysed [1,5] sigmatropic rearrangement and Friedel–Crafts cyclisation provides a new route to variously functionalized tetracycles.

Quinizarinquinone (**1**) can be regarded as a fundamental building block of natural antitumour substances such as adriamycin and daunomycin.¹ The recent report that the 4-demethoxy derivatives show markedly enhanced antitumour activities compared with their natural counterparts² has stimulated utilization of (**1**) and its analogues in anthracycline syntheses.^{3–7} However, most work in this field has dealt with Diels–Alder reactions using (**1**) as a dienophile, which sometimes required manipulation to achieve the desired

site-selectivity.^{5–10} We now report a new approach to the facile construction of linear tetracycles, with a complete demethoxydaunomycinone skeleton, *via* Michael-type reaction of (**1**) with *O*-silylated ketene acetals followed by sigmatropic rearrangements and Friedel–Crafts cyclisation.

Despite its seemingly enhanced electrophilic nature,¹¹ electrophilic reactions of (**1**) have received relatively little attention. We have found that (**1**) and *O*-silylated ketene acetals smoothly undergo a site-selective conjugate addition at

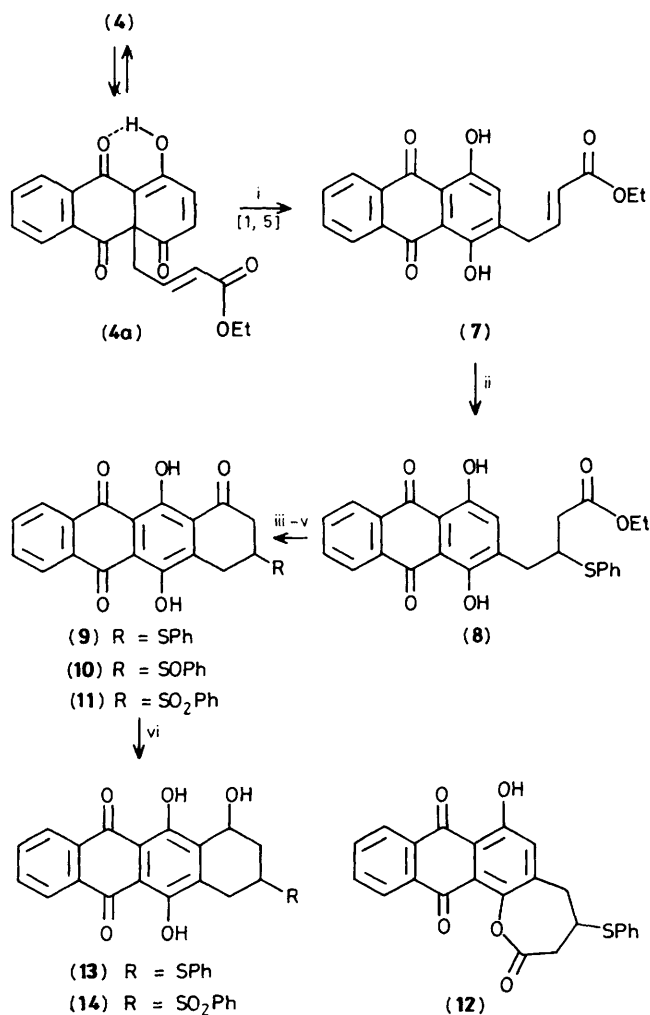


Scheme 1. Reagents and conditions: i, C_6H_6 , 80 °C (51%), ii, $Na_2S_4O_4$, DMF- H_2O (3:1), 70 °C (63%).

the internal double bond of (1) to give adducts of type (3). For example, the reaction of (1) and the acetal (2)¹² (CH_2Cl_2 , -50 °C, 30 min) followed by acid treatment (5% HCl) afforded the Michael-type adduct (4)[†] in 65% yield: m.p. 101–102.5 °C; i.r., ν_{max} 1710 and 1635 cm^{-1} ; 1H n.m.r., δ ($CDCl_3$) 14.89 (s, 1H), 7.09 (d, J 10.2 Hz, 1H), 6.57 (d, J 10.2 Hz, 1H), 6.55 (dt, J 15.6, 7.8 Hz, 1H), and 5.65 (dd, J 15.6, 1.5 Hz, 1H).

The adduct (4) underwent diverse rearrangements, depending upon the reaction conditions. Heating of (4) in refluxing benzene resulted in a [3,3] sigmatropic rearrangement to give (5)[†] (51%) [m.p. 120–121.5 °C; 1H n.m.r., δ 13.03 (s, 1H), 7.34 and 7.21 (ABq, J 8.0 Hz, 2H), and 5.17 (dm, J 4.8 Hz, 1H)], which further underwent a reductive Claisen rearrangement¹³ [$Na_2S_2O_4$, dimethylformamide (DMF)- H_2O (3:1), 70 °C] to (6)[†] (63%) [m.p. 111–113 °C; 1H n.m.r., δ 13.42, 13.40 (each s, 2H), 6.97 (dt, J 16.2, 7.2 Hz, 1H), and 5.94 (d, J 16.2 Hz, 1H)]; (5) was inert under the same conditions without $Na_2S_2O_4$ (Scheme 1). In contrast, treatment of (4) with $BF_3 \cdot OEt_2$ in dry CH_2Cl_2 (0 °C) led to smooth formation of (7)[†] (65%) [m.p. 140–141 °C; 1H n.m.r., δ 13.28, 12.83 (each s, 2H), 7.12 (dt, J 15.6, 6.6 Hz, 1H), 7.11 (s, 1H), 5.91 (d, J 15.6 Hz, 1H)] probably via [1,5] sigmatropic rearrangement of (4a), since similar treatment of (5) did not give (7a) (Scheme 2).

Both (6) and (7) could be transformed easily into tetracyclic systems as follows (Scheme 2). Treatment of (7) with $PhSH-Et_3N$ ($CHCl_3$, 25 °C) gave (8)[†] (79%), m.p.



Scheme 2. Reagents and conditions: i, $BF_3 \cdot OEt_2$, CH_2Cl_2 , 0 °C (65%); ii, $PhSH$, Et_3N , $CHCl_3$, 25 °C (79%); iii, HCl, AcOH, 110 °C (96%); iv, $(CF_3CO)_2O$, CF_3CO_2H , 25 °C (quant.); v, MCPBA, CH_2Cl_2 , 0 °C for (10) (quant.), 40 °C for (11) (quant.); vi, $NaBH_4$, $CeCl_3 \cdot 7H_2O$, CH_2Cl_2 -MeOH, 0 °C [(13): 97%, (14): 95%].

214–217 °C, which was also obtained in good yield by the similar reaction of (6) with concomitant oxidation. After acid hydrolysis of (8), attempted Friedel-Crafts cyclisation using acetic anhydride (25 °C, 1 day) led only to the seven-membered lactone (12)[†] (44%). However, change of the reagents to $(CF_3CO)_2O$ - CF_3CO_2H resulted in quantitative formation of the desired tetracyclic ketone (9)[†] [m.p. 190–193 °C, i.r., ν_{max} 3400, 1680, 1625, and 1585 cm^{-1} ; 1H n.m.r., δ 13.37, 12.88 (each s, 2H), 3.88–4.16 (m, 1H), and 2.76–3.35 (m, 4H)]. Compound (9) could be converted easily into the corresponding sulfoxide (10)[†] and sulphone (11)[†] by *m*-chloroperbenzoic acid (MCPBA) oxidation (1 and 2 equiv., respectively). Selective reduction of (9) and (11) with $NaBH_4$ in the presence of $CeCl_3 \cdot 7H_2O$ gave (13)[†] (97%) and (14)[†] (95%), respectively.

The above new methods wherein quinizarinquinone is utilized as a Michael acceptor may provide a simple method for the construction of linear tetracycles containing key functionalities, which might be useful intermediates for

[†] All new compounds gave satisfactory analytical and spectral data.

synthesis of anthracyclinone and its analogues for assessment of their biological activities.

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