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

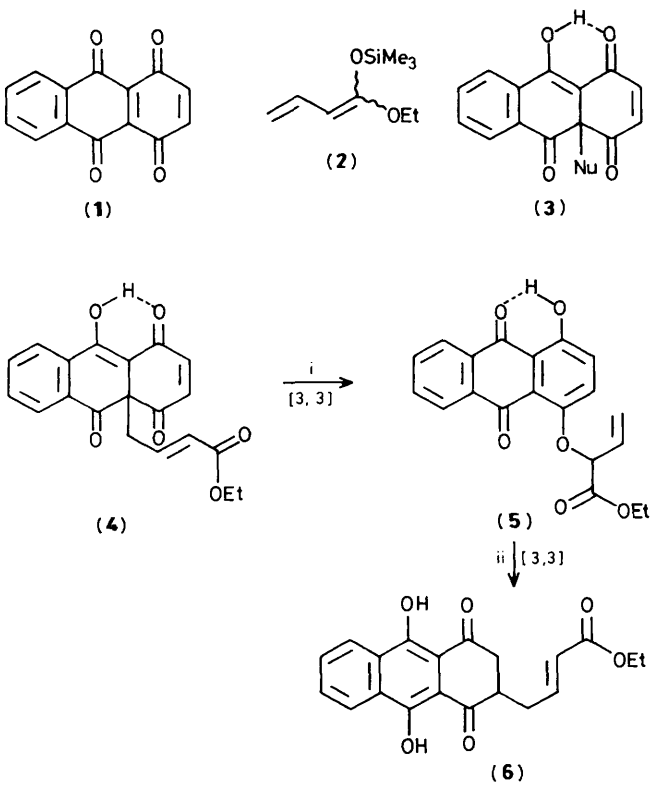
Kenji Hayakawa, Mariko Aso, and Ken Kanematsu*

Institute of Synthetic Organic Chemistry, Faculty of Pharmaceutical Sciences, Kyushu University 62, Maidashi, Higashi-ku, Fukuoka 812, Japan

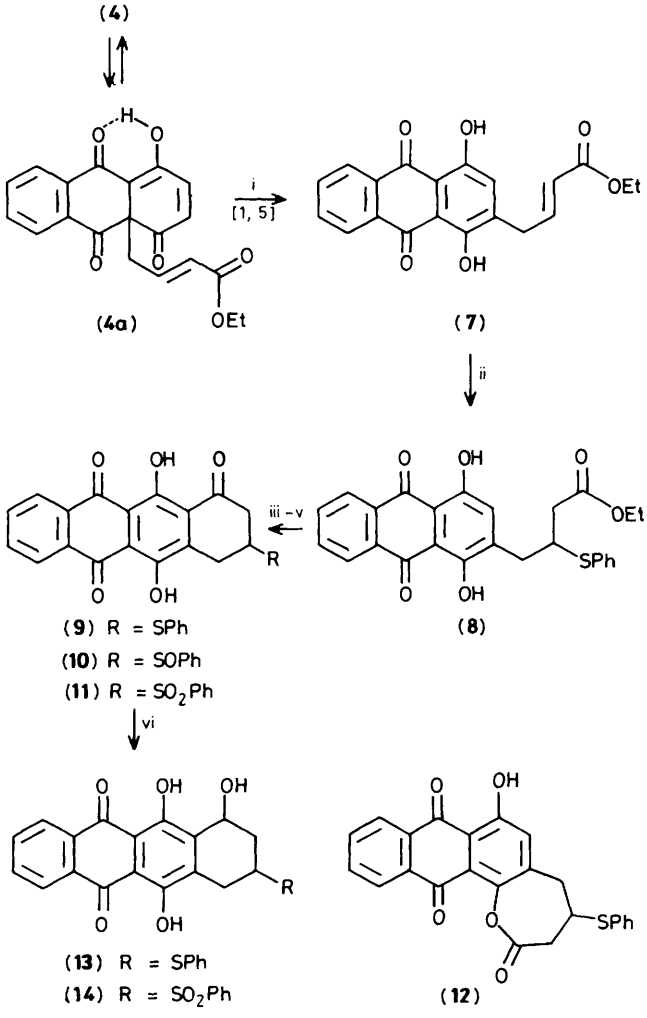
The Michael-type reaction of quinizarinquinone and 1-ethoxy-1-(trimethylsiloxy)buta-1,3-diene followed by Lewis acid-catalysed [1,5] sigmatropic rearrangement and Friedel–Crafts cyclisation provides a new route to variously functionalized tetracycles.

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 counterparts[2] 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%).



Scheme 2. *Reagents and conditions:* i, BF_3·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, $NaBH_4$, $CeCl_3$·$7H_2O$, CH_2Cl_2–MeOH, 0 °C [(**13**): 97%, (**14**): 95%].

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., $\nu_{max.}$ 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 rearrangement[13] [$Na_2S_2O_4$, 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·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. 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., $\nu_{max.}$ 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 sulphoxide (**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 $CeCl_3$·$7H_2O$ 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.

Received, 12th August 1986; Com. 1158

References

1 H. S. El Khadem, 'Anthracycline Antibiotics,' Academic Press, New York, 1982.
2 F. Arcamone, L. Bernardi, P. Giardino, B. Patelli, A. DiMarco, A. M. Casazza, G. Pratesi, and P. Reggiani, *Cancer Treatment Rep.*, 1976, **60**, 829.
3 W. W. Lee, A. P. Martinez, T. H. Smith, and D. W. Henry, *J. Org. Chem.*, 1976, **41**, 2296.
4 R. B. Garland, J. R. Palmer, J. A. Schulz, P. B. Sollman, and R. Pappo, *Tetrahedron Lett.*, 1978, 3669.
5 T. R. Kelly and W.-C. Tsang, *Tetrahedron Lett.*, 1978, 4457.
6 R. C. Gupta, D. A. Jackson, R. J. Stoodley, and D. J. Williams, *J. Chem. Soc., Perkin Trans. 1*, 1985, 525; M. Chandler and R. J. Stoodley, *ibid.*, 1980, 1007.
7 A. S. Kende, Y.-G. Tsay, and J. E. Mills, *J. Am. Chem. Soc.*, 1976, **98**, 1967; A. S. Kende, D. P. Curran, Y. Tsay, and J. E. Mills, *Tetrahedron Lett.*, 1977, 3537.
8 R. N. Warrener, D. A. C. Evans, and R. A. Russell, *Tetrahedron Lett.*, 1984, 4833.
9 R. P. Potman, F. J. van Kleef, and H. W. Scheeren, *J. Org. Chem.*, 1985, **50**, 1955.
10 P. N. Preston, T. Winwick, and J. O. Morley, *J. Chem. Soc., Perkin Trans. 1*, 1985, 39.
11 S. Yoshino, K. Hayakawa, and K. Kanematsu, *J. Org. Chem.*, 1981, **46**, 3841; K. Hayakawa, M. Aso, and K. Kanematsu, *ibid.*, 1985, **50**, 2036.
12 I. Fleming, J. Goldhill, and I. Paterson, *Tetrahedron Lett.*, 1979, 3205.
13 I. K. Boddy, P. J. Boniface, R. C. Cambie, P. A. Craw, D. S. Larsen, H. McDonald, P. S. Rutledge, and P. D. Woodgate, *Tetrahedron Lett.*, 1982,4407.