Tetrahedron Letters, Vol. 34, No. 38, pp. 6109-6110, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Synthesis of Naphthacenequinones by Cycloaddition and Deoxygenation Methodology: Synthesis of SS-228R

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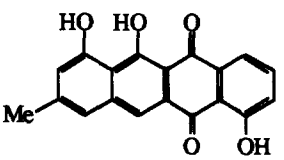
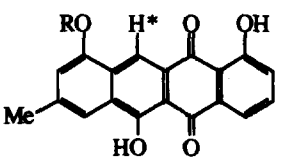
Abstract: The tetracycle SS-228R (2) has been synthesised by a short regioselective sequence based on cycloaddition and novel deoxygenation of an intermediate naphthacenequinone.

The structure of the naphthacenequinone SS-228R derived from the photolabile antibiotic SS-228Y has been the subject of discussion, resulting in its revision from (1)[1] to the isomeric structure (2)[2] based on biosynthetic grounds. This uncertainty of structure has led to synthetic interest in the naphthacenequinones (1) and (2). Thus, the correct structure of SS-228R was established as (2) by two independent syntheses as well as by separate syntheses of the regioisomer (1).[3,4]



(1)

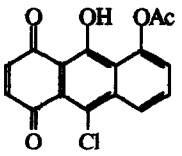


(2) R = H
(7) R = Me

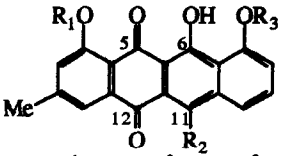
This communication details a short synthesis of SS-228R (2) using cycloaddition methodology of 1,4-anthraquinones, to generate naphthacenequinones. The key step is the novel deoxygenation of a naphthacenequinone using catalytic reduction followed by oxidation with *p*-chloranil.

The starting point for this synthesis was the known 1,4-anthraquinone (3) available by a two-step process from the dyestuff 1,4,5-trihydroxy-9,10-anthraquinone.[5] Cycloaddition of 1-methoxy-3-methyl-1-trimethylsilyloxy-1,3-butadiene followed by controlled aromatization[3], involving DDQ oxidation of the cycloadduct, gave the methyl ether (4) (71%), m.p. 273-274° [δ_{OH} (CD_2Cl_2) 16.34] together with the corresponding hydroxy derivative (5) (26%), m.p. 255-256.5°. This expected regiochemistry of cycloaddition[5] was confirmed by the observation of both free and chelated quinone carbonyl groups in the i.r. spectrum of (5) [ν_{max} 1675 and 1625 cm^{-1}, respectively]. Furthermore, the chemical shifts for the two hydroxy resonances of (5) [δ15.32 and 11.83] agreed satisfactorily with reported values for the model chromophore 6-chloro-1,11-

dihydroxy-5,12-naphthacenequinone [δ15.47, 12.04].[6] The regiochemical parallel between the methyl ether (4) and the diol (5) was confirmed by selective methylation of the latter (MeI/Ag_2O) to give the former (37%).



(3)



(4) R^1 = Me, R^2 = Cl, R^3 = Ac
(5) R^1 = H, R^2 = Cl, R^3 = Ac
(6) R^1 = Me, R^2 = OH, R^3 = H

Replacement of the chloro group in (4) by an oxygen substituent was achieved smoothly by treatment with trifluoroacetic acid (140°), which afforded the naphthacenequinone (6) (78%), m.p. 275.5-277° [δ_{OH} 15.60, 15.52, and 12.43]. Molecular modelling studies[7] indicated that the 5,12-dione tautomer (6) was more stable than the alternative 6,11-dione, a crucial feature for subsequent modification.

Catalytic reduction or hydride reduction followed by reoxidation has been used to selectively deoxygenate a quinone carbonyl group *peri* to a methoxy substituent in quinizarin-based systems.[3,8] However, this methodology had not been extended to napthacenequinones. Accordingly, hydrogenation of (6) over PtO_2 in ethyl acetate followed by reoxidation of the crude product with *p*-chloranil gave the dihydroxynaphthacenequinone (7) as the only isolatable product (20%), m.p. 293-295° [δ_{OH} 14.52, 13.09; δ_{H^*} 8.74]. The assigned regiochemistry of formation of (7) followed from the observation of only chelated carbonyl groups in its i.r. spectrum [$\nu_{C=O}$ 1630 cm^{-1}].[9] Furthermore, the considerable deshielding of H* is indicative of an aromatic proton *peri* to a carbonyl and a methoxyl group.[3,8]

Demethylation of (7) with boron tribromide in dichloromethane gave SS-228R (2) (75%), dec. >298° [δ_{H^*} C_5D_5N 9.28] which was identical with material previously prepared by alternative methodology.[3]

All new compounds gave satisfactory analyses and spectroscopic data, except for (7) (exact mass). We thank Dr P. G. Griffiths for useful discussion, and Miss L. Cardle and Dr D. C. Nonhebel for assistance with the molecular modelling.

REFERENCES AND NOTES

1. Kitahara, T.; Naganawa, H.; Okazaki, T.; Okami, Y. and Umezawa, H., *J. Antibiot.*, **1975**, *28*, 280.
2. Imamura, N.; Kakinuma, K.; Ikekawa, N.; Tanaka, H. and Omura, S., *J. Antibiot.*, **1982**, *35*, 602.
3. Cameron, D. W.; Feutrill, G. I.; Gibson, C. L. and Read, R. W., *Tetrahedron Lett.*, **1985**, *26*, 3887.
4. Tamura, Y.; Fukata, F.; Sasho, M.; Tsugoshi, T. and Kita, Y., J. Org. Chem., **1985**, *50*, 2273.
5. Cameron, D. W.; Feutrill, G. I.; Griffiths, P. G. and Merrett, B. K., *Tetrahedron Lett.*, **1986**, *27*, 2421.
6. Carretero, J. C.; Cuevas, J. C.; Chavarren, A. E.; Prados, P and Fariña, F., *J. Chem Res. (M)*, **1984**, 0147.
7. Molecular mechanics calculations using PCMODEL (4.40) with a Macintosh LCII (plus co-processor) indicated that the heat of formation for the 5,12-dione (6) was lower than the 6,11-dione tautomer by 47 kJ/mol.
8. Cameron, D. W. and de Bruyn, P. J., *Tetrahedron Lett.*, **1992**, *33*, 5593.
9. Reduction of the alternative 12-carbonyl group in (6) and reoxidation would result in a product with one free and one chelated quinone carbonyl.

(Received in UK 4 June 1993; accepted 23 July 1993)