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Synthesis of 2-sulphur-substituted 1,4-anthraquinones. Application to the Synthesis of Anthracyclinone Precursors

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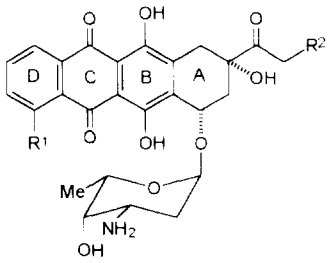
Abstract 2-sulphur-substituted 1,4-anthraquinones **8a,b** and **10** have been prepared by annelation reactions of the anions of furanones **5a,b** with naphthoquinone monoketals of type **6** and **9**. Diels-Alder reaction of the 1,4-anthraquinones **11a,b** with (*E*)-1,3-bis(trimethylsilyloxy)buta-1,3-diene (**12**) affords ABCD tetracyclic systems related to those existing in anthracyclinones.

The efficacy of anthracycline antibiotics such as daunomycin (**1**) and adriamycin (**2**) in the treatment of a variety of human cancers has stimulated a continued interest in the synthesis of this class of antitumor agents.[1] However, these compounds display various side effects, the most serious being a cumulative dose-dependent cardiotoxicity, so that considerable efforts have been devoted to develop new structurally modified anthracyclines with an improved antineoplastic activity and a low cardiotoxicity. It is also well known that the synthetic 4-demethoxy derivatives of daunomycin and adriamycin (**3**, **4**) are more effective antitumor agents than the parent compounds.[2]



1: R^1=OMe , R^2=H
2: R^1=OMe , R^2=OH
3: R^1=H , R^2= H
4: R^1=H , R^2=OH

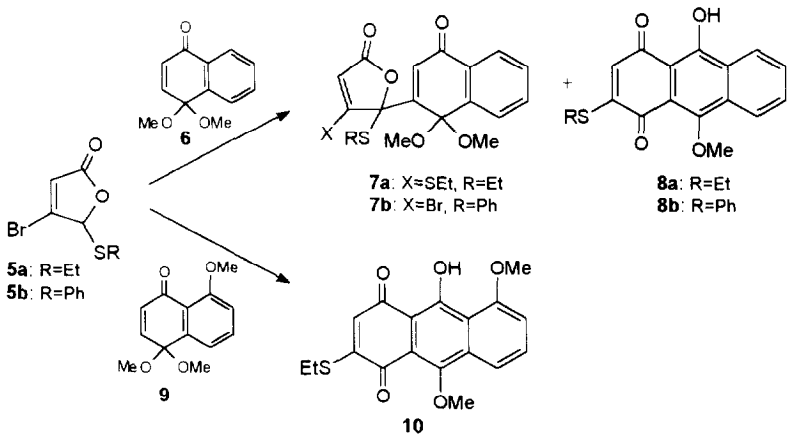
As a part of a general development of new approaches to compounds related to anthracyclinones, we have been exploring the synthesis of BCD synthons that allows the construction of the tetracyclic system of type **1** and **3** in a subsequent Diels-Alder reaction. In preceding papers[3] we have reported the first total synthesis of 5-iminodaunomycinone and its 4-demethoxy derivative. In our strategy, the key step is a regiocontrolled Diels-Alder reaction of an adequately 1,3-disubstituted buta-1,3-diene with fixed derivatives of the 1,4-anthraquinonoid tautomer of 1,4-dihydroxy-9,10-anthraquinone imines, as suitable BCD-ring synthons.

It was therefore of interest to study the synthesis of 1,4-anthraquinones of type **8** and **10**, in which the introduction of a sulphur bearing group at 2-position, could be used to control the regiochemistry of the Diels-Alder cycloaddition.

On the other hand, our previous results[4] show that annelation reactions of anions generated from furan-2(5*H*)-ones substituted at 5-position by sulphur bearing groups such as SEt, SPh, SO_2Et and SO_2Ph, with several napthoquinone monoketals led exclusively to the Michael adduct, without subsequent ring closure to the anthraquinones. However, we have now found that the required 1,4-anthraquinones can be obtained, by annelation reactions of anions of 4-halo-5-sulphur-furan-2(5*H*)-ones of type **5** with naphthoquinone monoketals.

This paper report a novel route to the synthesis of differently substituted 1,4-anthraquinones, their Diels-Alder reaction and investigations about the subsequent conversion of cycloadducts into compounds related to anthracyclinones.

Reaction of the anion generated from 4-bromo-5-ethylthiofuran-2(5*H*)-one (**5a**)[5] with lithium diisopropylamide, at -78°C in tetrahydrofuran, with naphthoquinone monoketal **6**,[6] after 7 days, at -7°C, afforded a 45:55 mixture of diastereoisomeric Michael adducts **7a**[7] and the 1,4-anthraquinone **8a**[8] in a 15% and 45% yield respectively (Scheme 1). It is noteworthy that simultaneously to the annnelation reaction takes place the substitution of a bromine atom by the ethylthio group.



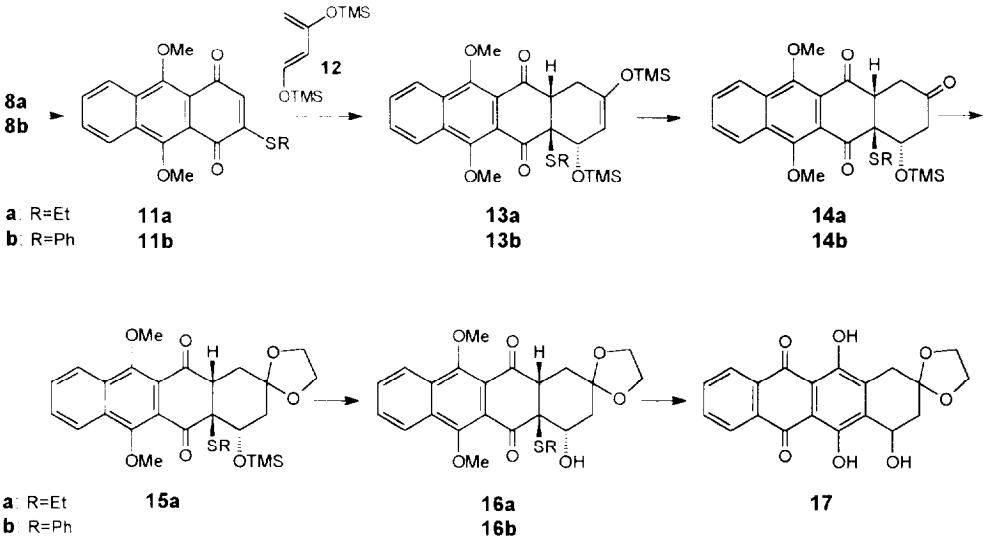
Scheme 1

Under similar reaction conditions, the anion of 4-bromo-5-phenylthiofuran-2(5*H*)-one (**5b**)[9] reacted with monoketal **6** to afford, after 13 days, a 60:40 mixture of diastereoisomeric Michael adducts **7b** (10%) and the 1,4-anthraquinone **8b**[10] (50%). However, the annelation reaction between the anion of **5a** with monoketal **9** led exclusively to the 1,4-anthraquinone **10**[11] in 40% yield (Scheme 1).

Methylation of the 1,4-anthraquinones **8a** and **8b** with methyl iodide, in the presence of silver oxide, gives the corresponding dimethyl ethers **11a** and **11b** in 95% yield.

Our first attempts to reaction of Diels-Alder between the 1,4-anthraquinones **8a,b** and an appropiate 1,3-disubstituted diene such as (*E*)-1,3-bis(trimethylsilyloxy)buta-1,3-diene (**12**), in benzene under reflux, over a period of 15 days, failed to give the expected adducts.

However, Diels-Alder reaction of the anthraquinone **11a** with diene **12** (benzene, 60°C, 12 days) occurs regio- and stereo-specifically to afford the adduct **13a**[12] (87%), which without purification was subject to a mild acidic treatment (HCl, THF, 0°C, 5 min) to give the tetracyclic ketone **14a** (95%) by selective hydrolysis of the silyl enol ether (Scheme 2).



Scheme 2

Then, it was necessary to protect the keto group as the ethylene dioxyderivative **15a**, which was prepared from **14a** by treatment with ethylene glycol in presence of *p*-toluenesulphonic acid (benzene, 80°C, 12 h) in 97% yield. Subsequent treatment of the ketal **15a** with tartaric acid in THF at room temperature yielded **16a** in 95%. The following steps of the synthesis were directed to obtain the appropriate A-ring functionality. Thus, oxidative demethylation of **16a** with silver(II) oxide, yielded the previously reported[13] quinone **17** (85%). It is noteworthy, that under the reaction conditions takes places the removal of EtSOH.

For the synthesis of the quinone **17**, an comparable sequence is followed from 4-bromo-5-phenylthiofuran-2(5*H*)-one (**5b**). The sequence **5b→8b→11b→13b→14b→16b→17** afforded the tetracyclic system **17** (25% overal yield), in only six laboratory operation from **5b** (Scheme 2).

In summary, we have develop a novel procedure for the synthesis of 1,4-anthraquinones, starting from furanones and naphthoquinone monoketals. The synthetic methodology described herein, that uses the anthraquinones **11a,b** as suitables BCD ring synthon, may also be relevant for the construction of novel unnatural anthracyclinones.

Acknowledgment

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6. For the synthesis of naphthoquinone monoketals see: Fariña, F.; Paredes, M.C.; Soto, J.J. *An. Quim.* **1995**, *91*, 50.
7. All new compounds gave satisfactory spectral data (IR, NMR and MS). Satisfactory combustion analyses were obtained for compounds **7a**, **8a,b**, **10**, **11a,b**, **14b** and **16b**.
8. Compound **8a**: ^{1}H NMR δ 14.85 (s, 1H), 8.50-8.48 (m, 1H), 8.35-8.31 (m, 1H), 7.78-7.73 (m, 2H), 6.63 (s, 1H), 4.03 (s, 3H), 2.87 (q, 2H), 1.45 (t, 3H).
9. Alguacil, R.; Fariña, F.; Martín, M.V. unpublished results.
10. Compound **8b**: ^{1}H NMR δ 14.71 (s, 1H), 8.43-8.40 (m, 1H), 8.38-8.30 (m, 1H), 7.72-7.66 (m, 2H), 7.52-7.43 (m, 5H), 6.08 (s, 1H), 4.0 (s, 3H).
11. Compound **10**: ^{1}H NMR δ 16.04 (s, 1H), 7.94 (d, 1H), 7.68 (t, 1H), 7.14 (d, 1H), 6.62 (s, 1H), 4.06 (s, 3H), 3.98 (s, 3H), 2.86 (q, 2H), 1.44 (t, 3H).
12. The structure was conclusively established on the basis of its ^{1}H NMR spectrum, in which the methine proton on the carbon bearing the OTMS (C-7) appears as a doublet (δ 4.62, J=6.0 Hz) coupled with the olefinic proton.
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