Regiospecific Synthesis of Bis(quinone monoacetals) and their Annelation to give Bisanthraquinones

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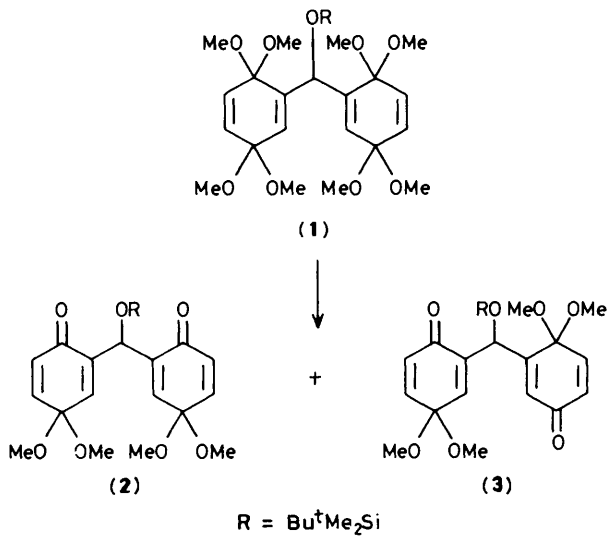
The anodic oxidation of bis-(*p*-methoxyphenol) derivatives bearing methoxymethyl, methoxyethoxymethyl, or t-butyldimethylsilyl protecting groups affords regiospecifically bis-dienones which can be annelated with anions derived from 3-cyanophthalides to yield bisanthraquinones and bisanthracyclinones.

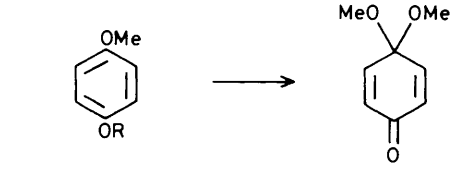
The value of bis-intercalating molecules as antineoplastic agents has engendered interest in the synthesis of a variety of such compounds. Most activity has centered on linked acridines and other simple intercalator molecules;[1] more recently a few bis-intercalators have been prepared by linking together naturally occurring anthracyclines such as the known antitumour agent daunomycin.[2] As part of a programme to study the pharmacological activity and mode of action of anthracycline bis-intercalators, we required a general synthetic route for their production, especially one able to incorporate n.m.r. labels in the intercalating moiety.

Our approach to the synthesis of bis-intercalators involved the use of linked quinone monoacetals (bis-dienones) as key intermediates, since they offered entry into anthraquinones[3] and anthracyclines *via* their reaction with cyanophthalide anions.[4] A variety of substituted or labelled phthalides[5] are known to undergo this type of condensation, which has the advantage of proceeding in high yield and with full regiochemical integrity.

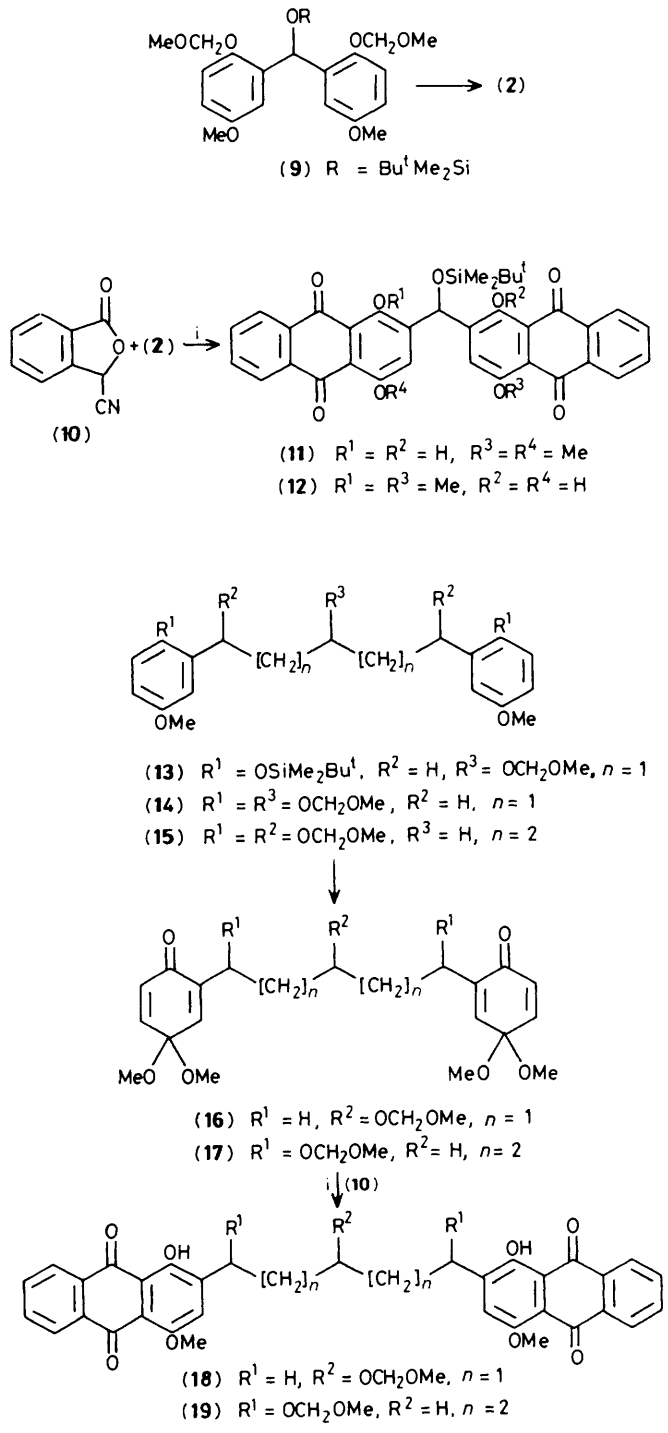
The success of this method depended on our ability to produce the intermediate bis-dienones regiospecifically.



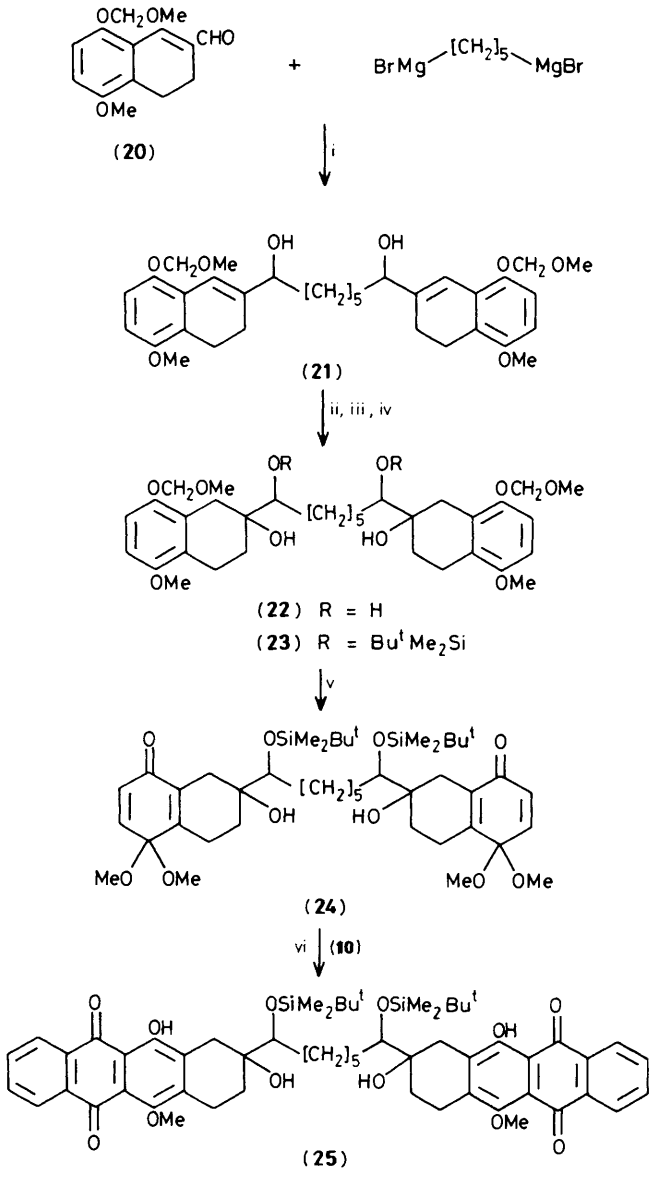
Scheme 1



(4) R = Me_3Si
(5) R = Bu^tMe_2Si
(6) R = $MeOCH_2$
(7) R = $MeO[CH_2]_2OCH_2$



Scheme 2. *Reagents*; i, lithium di-isopropylamide (LDA), tetrahydrofuran (THF), −78 °C.



Scheme 3. *Reagents:* THF room temp.; ii, VO(acac)$_2$ t-butyl hydroperoxide, benzene; iii, lithium aluminium hydride, THF; iv, t-butyldimethylsilyl chloride, ethyldi-isopropylamine, dimethylformamide; v, anodic oxidation; vi, LDA, THF, − 78 °C.

Experiments showed that selective hydrolysis of linked bis-acetals, in contrast to the reaction of simple bis-acetals,[6] was non-specific and produced a mixture of symmetrical and unsymmetrical bis-dienones (Scheme 1). Notably the model tetra-acetal (**1**) in which the protected hydroxy group of the linking chain was positioned to aid selectivity, still produced a mixture of isomeric linked dienones (**2**) and (**3**) under hydrolysis conditions.

In view of this result, we developed a new route to dienones employing electrochemical oxidation of protected *p*-methoxyphenols to achieve regioselectivity. The advantage of this method rests on the selective removal of the phenol-protecting group in the course of the electrochemical oxidation.† *O*-Trimethyl silyl[7] (**4**), t-butyldimethylsilyl[7] (**5**), methoxymethyl (**6**), and methoxyethoxymethyl (**7**) derivatives enter this reaction with equal facility, thus allowing a wide selection

† Electrochemical oxidations were conducted in a divided cell using platinum electrodes and an anhydrous electrolyte mixture containing lithium perchlorate and sodium acetate in anhydrous methanol. The anode potential of 1.3 V was referenced to a standard calomel electrode and the anode compartment purged with argon for the duration of the reaction. This procedure has been found to be generally applicable to substrates sensitive to methanolic KOH and is a valuable variation of conditions for anodic oxidations.

of reaction conditions to be encompassed in the preparation of more complex dienone precursors.

Application of this method to the regioselective synthesis of the symmetrical bis-dienone (**2**)‡ was readily achieved from the linked methoxymethyl ether (**9**);§ significantly the *O*-t-butyldimethylsilyl group in the side chain remained intact. Condensation with the anion of cyanophthalide (**10**) produced the linked anthraquinone (**11**) in good yield. Similarly the bis-dienone (**3**) afforded the quinone (**12**). Further examples are provided by the regiospecific preparation of the bis-dienones (**16**) and (**17**), used in the preparation of the linked anthraquinones (**18**) and (**19**), respectively (Scheme 2). Here both methoxymethyl and t-butyldimethylsilyl groups have been used for protection of the phenol, and each route can tolerate methoxymethyl protecting groups on the linking chain.

The final example relates to the synthesis of linked anthracyclinones and is illustrated by conversion of the bis-bicyclic dienone (**24**) into the bisanthracyclinone (**25**). The synthesis of (**24**) was achieved as outlined in Scheme 3 and was conducted at the racemic level. This and the foregoing examples clearly demonstrate that the method can be applied to compounds having extended carbon chains in the link and that *O*-methoxymethyl and t-butyldimethylsilyl protecting groups can be incorporated therein.

The extension of this methodology to the total synthesis of linked anthracyclines related to daunomycin is our next goal.

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‡ Bis-dienones were routinely obtained in crude yields of > 80%; the products were used directly owing to their sensitivity to chromatographic media.

§ Satisfactory ^{1}H n.m.r., i.r., and mass spectra were obtained for all new compounds. All compounds were oils or foams with the exception of (**11**), m.p. 243—245 °C, and (**12**), m.p. 127—129 °C.

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