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NEW STRATEGY FOR THE SYNTHESIS OF KEY ANTHRACYCLINE PRECURSORS

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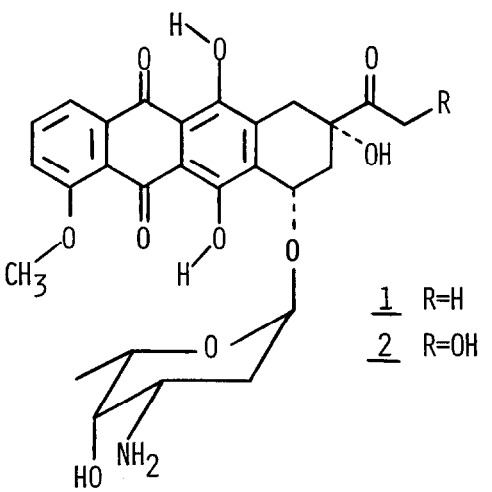
Abstract: *A novel, practical approach to the synthesis of anthracyclines precursor 3 was developed. It centers on the use of the new ketimine synthon 7.*

The clinical usefulness as antitumor agents[1] of the anthracycline antibiotics daunomycin (1) and adriamycin (2), obtained in low yield by fermentation[2], has stimulated much research on synthetic methods[3] for the generation of these natural products. The dose-dependent cardiotoxicity[4] of these agents imposes severe restrictions on their utilization in cancer treatment and as a result much interest is currently attached to synthetic methodology capable of generating new analogs potentially devoid of this limiting toxicity.

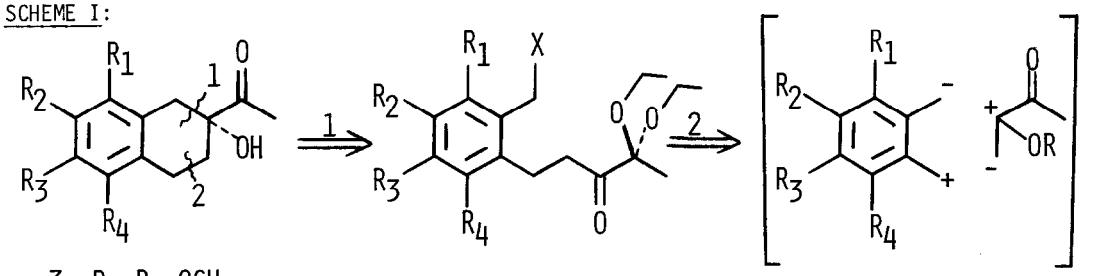
A synthetic strategy allowing for the ready preparation of a variety of these products and structural analogues from a common synthon would have considerable practical potential from the medicinal chemical point of view. We wish to describe such a new synthetic methodology based on an annulation reaction leading to the key α-hydroxyketone moiety from a substituted dialkyl arene. This new approach is exemplified by the synthesis of the known (±)-2-acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol (3), itself a key intermediate in several syntheses[3] of the anthracyclines and their analogues.



1 R=H
2 R=OH

Our retrosynthetic analysis (Scheme I) of key intermediate 3 led us to the novel theoretical fragmentation pattern shown as 5 which is formally equivalent to combining a biacetyl anion with an electrophilic benzyl carbon followed by nucleophilic attack of a biacetyl carbonyl by another adjacent benzyl carbon. In practice, this strategy calls for

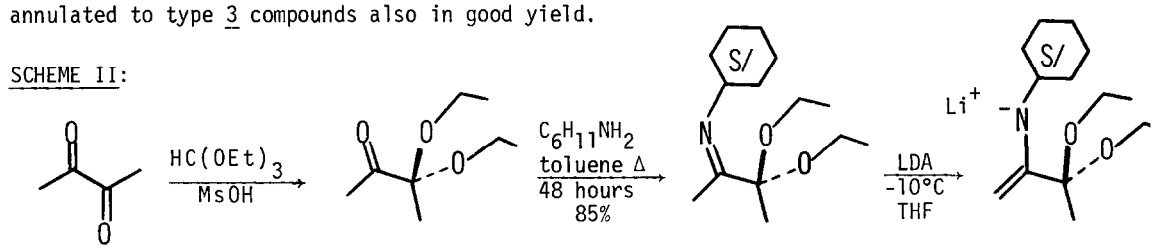
SCHEME I:



3 $R_1=R_4=OCH_3$, $R_2=R_3=H$ 4 5

the generation of an anionic biacetyl synthon suitable for mono-alkylation by an ortho bis-halomethylarene followed by intramolecular ring closure through a Grignard-like intermediate. This meant that an intermediate of type 4 (X = halogen) may be obtainable from a biacetyl synthon and transformable to the desired key intermediate 3 by way of a Grignard reaction. After extensive experimentation[5], the lithioenamine 8 was found suitable under selected conditions for the production in good yield of type 4 intermediates which in turn could be annulated to type 3 compounds also in good yield.

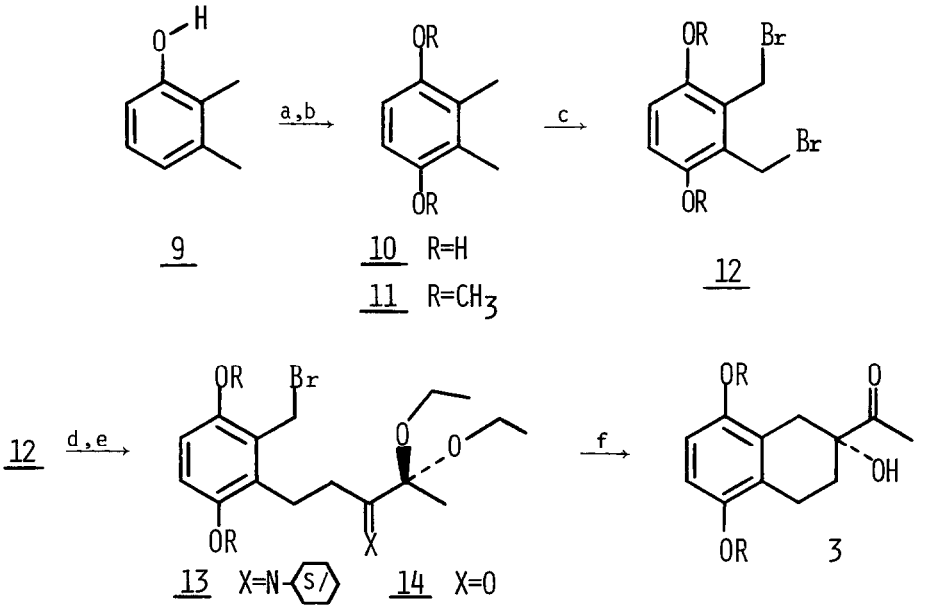
SCHEME II:



6 7 8

Thus, biacetyl was converted to monoketal 6[6,7] which yielded ketimine 7[7a,8] with cyclohexylamine (Scheme II). Reaction of 7 with LDA at -10° gave the desired 8. The ortho bis-halogenomethyl fragment was readily prepared from 2,3-dimethylhydroquinone 10[7,9] (Scheme III). It was O-methylated to 11[7,10] (95%) followed by bromination to 12 in the usual manner[7,10,11]. Slow addition (30 min) of lithioenamine 8 (1 eq) to a THF solution of dibromide 12 at -78° followed by stirring for 3 h while allowing the temperature to reach 23° led to 13[7a] which was not isolated but hydrolyzed during work-up through the addition of oxalic acid (1.1 eq) followed by partitioning between CH_2Cl_2 and 0.1 N aqueous oxalic acid. The crude product was purified by flash chromatography to give ketone 14[7a] in 65-70% yields. Dibromide 12 (10-15%) and dialkylated material 15[7a] were also isolated. The intramolecular ring closure was best accomplished by slow addition of bromoketone 14 to a vigorously stirred THF suspension (argon)

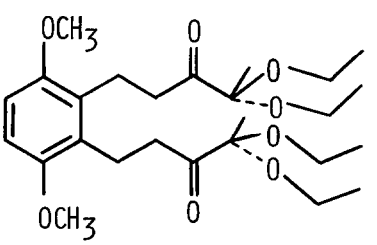
SCHEME III:



a) Reference 9; b) K_2CO_3, Me_2SO_4, reflux acetone, 95%; c) NBS, AIBN, $CCl_4\Delta$, 90%; d) LDA, THF, 8; e) $(CO_2H)_2/H_2O$, 65-70%; f) Mg*, THF, RT/2N HCl, 70%.

of Mg[12] (3-4 eq). After stirring for 17 h, the mixture was hydrolyzed (2N HCl) to give after work-up the known key intermediate 3[7,13a] in 70% yield.

The above methodology compares quite favorably as regards efficiency and expediency to other reported syntheses[13] of 3. Problems associated with α-hydroxylation of an intermediate methyl ketone as well as formation of the latter are avoided by the incorporation of these functionalities in latent form in synthon 8. The general ready availability of ortho bis-halomethylarene intermediates (where R_1-R_4 in 3 may form part of some complex structures) makes the above approach attractive for the generation of naturally occurring anthracyclines and especially nuclear analogues as we shall report later.



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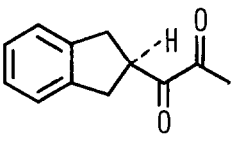
5. Utilization of 1 eq of lithium enolate of 6 at -78°C with α,α'-dibromo-o-xylene produced 16[7a] after acid hydrolysis. In our hands, other methods using triethanolamineborate[14], α-tributylstannyl ketones[15] and enol silyl ethers of 6 with ammonium fluorides[16] were ineffective in obtaining 14.



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7. a) NMR, IR and mass spectra in complete agreement with the assigned structure;
   b) Identical in all respects to literature values.
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12. a) Best results were obtained with magnesium prepared by the reduction of $MgCl_2$ with sodium naphthalide[12b]. Other forms of magnesium or lithium metal were less effective.
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