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A GENERAL ROUTE TO 11-DEOXYANTHRACYCLINES

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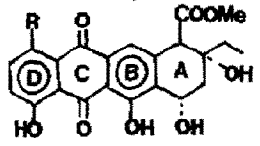
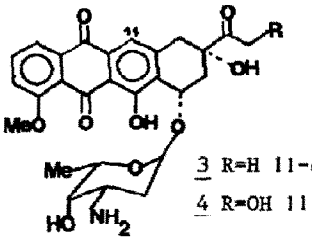
Summary - Diels-Alder type cycloaddition of unsaturated ketene acetal 5 with various naphtoquinones affords a short and regiospecific access to tetracyclic ketones, key intermediates for the further synthesis of 11-deoxyanthracyclines.

Anthracycline antibiotics are presently of great interest due to the effectiveness of some members of this large family (i.e doxorubicin, daunorubicin) in the clinical treatment of various cancers [1a-b]. Serious side effects as well as a limited supply of these drugs have encouraged numerous efforts toward their total synthesis[2]. However most of the published routes based on reactions which require the presence of two hydroxyl groups in ring B (Diels-Alder condensation of anthradiquinone with butadienes, Friedel-Crafts cycloacylation) cannot be used for the synthesis of 6 or 11-deoxyanthracyclines.

This latter group of antibiotics is particulary important : aclacynomycins[2a], compounds of the bohemic acid complex[2a] (whose aglycones respectively are aklavinone 1 and pyrromycinone 2) and nogalamycin[3] exhibit promising antitumor activity associated with a lower cardiotoxicity.



1 R=H aklavinone
2 R=OH pyrromycinone



3 R=H 11-deoxydaunorubicin
4 R=OH 11-deoxydoxorubicin

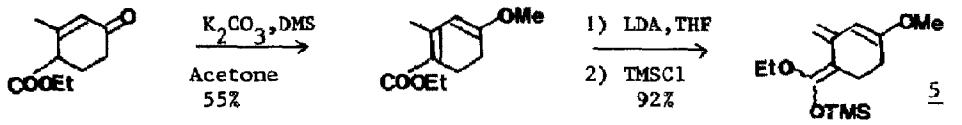
The recent isolation of 3 and 4 by Arcamone[4] and their reported activity further demonstrate that aglycone modification may be important to enhance the therapeutic index of these drugs.

We disclose here a general and regiospecific approach to 11-deoxyanthracyclines. The key step is a Diels-Alder type reaction of a substituted naphtoquinone A with diene 5 to give after air oxydation and hydrolysis the corresponding tetracyclic ketone B.

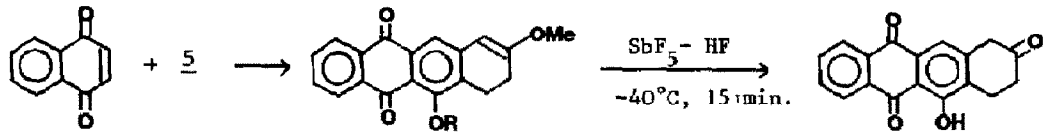
A R-H, OH, OR 5 B

These compounds were selected by analogy with Kende's intermediate in daunomycin and rhodomycin syntheses[2b] but our approach may also be extended to more functionalized dienes.

5 is readily accessible from commercially avalaible Hagemann ester by enol etherification followed by exocyclic deprotonation with L.D.A. and subsequent TMSCl quenching of the dienolate[5].



Reactions of 5 with various quinones were run at room temperature (or lower) in anhydrous solvents (THF, benzene, CH_2Cl_2) using equimolecular amounts of both reactants. After air oxydation in mild acidic conditions (0.1N HCl) the corresponding tetracyclic compounds are purified by column chromatography over Si gel or by crystallization. Preliminary experiments using naphtoquinone itself show that both phenol 6 and its ethyl ether 7 are obtained in about a 1:4 ratio without significant variations using different work-up procedures[6].

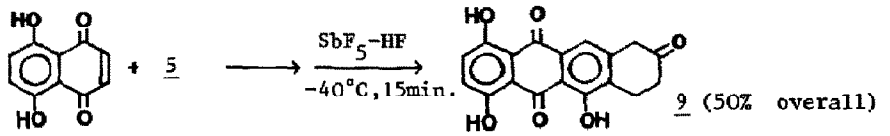


6 R=H; 7 R=Et

8

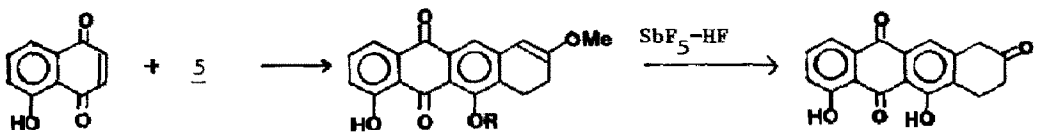
Conversion of the crude mixture (6 + 7) to 8 may be done in two steps using standard conditions[7]. However previous observations in this laboratory[8] that aryl ethyl ethers are rapidly cleaved at low temperature in SbF_5-HF (aryl methyl ethers are stable under similar conditions) suggest the use of this superacid. High solubility of these polyfunctional compounds and easy work-up leave in better overall yield (67% from naphtoquinone) the orange yellow ketone 8 m.p. 245-247°C[9].

Another example of condensation with a symmetrical quinone is illustrated by the synthesis of the red ketone 9, m.p. 251-253°C[9], from naphtazarin.



9 (50% overall)

Cycloaddition of 5 with unsymmetrical quinones such as juglone may be anticipated to be highly regiospecific following the hypothesis of Boeckman [10] that strongly polarized dienes are paramount to avoid mixture of isomers. This is confirmed by the formation of 10

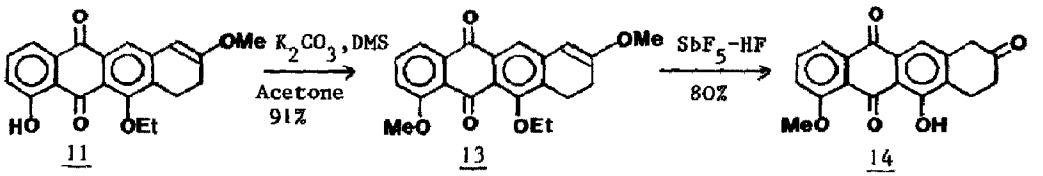


Juglone

10 R=H 18%; 11 R=C_2H_5 43%

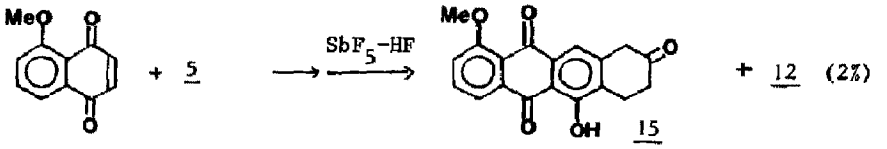
12 (40% overall)

and 11 from juglone in 61% yield. Treatment of the mixture with SbF_5-HF gives a single orange ketone 12, m.p. 241-242°C. Compound 11 may be easily separated from 10 by column chromatography over Si gel using CH_2Cl_2 (or benzene) as eluent ; methylation to 13 and hydrolysis with SbF_5-HF affords a single orange ketone 14, m.p. 258-259°C[9] in 31% yield from juglone.



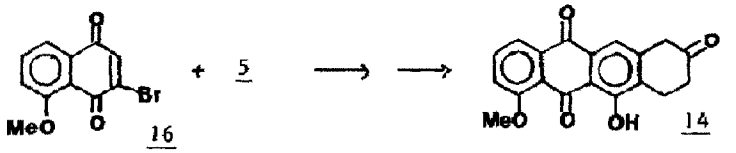
11 13 14

Cycloaddition of 5 with the methyl ether of juglone is more sluggish but affords after treatment of the crude mixture with SbF_5-HF, a 36% yield of ketone 15 m.p. 210-213°C[9] together with a small amount of 12, thus confirming the well-known reversal in cycloaddition orientation between juglone and its methyl ether[10].



15

The ring substitution pattern of the anthraquinone moiety in 14 may be also confirmed by reaction of 5 with 3-bromo 5-methoxy 1,4-naphtoquinone 16. After work-up and treatment with superacid only ketone 14 is isolated and detected by chromatography (55% overall yield).



This result is in agreement with the reported regiospecific cycloaddition of vinyl ketene acetals with haloquinones studied by Brassard and co-workers[11]. TLC examination of the crude mixture prior to hydrolysis reveals the presence of minor amounts of the aryl ethyl ether 13 beside the corresponding phenol (similar observations have also been made by Brassard[11]).

Thus cycloaddition of diene 5 with various quinones affords an expeditive and regiospecific synthesis of anthracycline intermediates. Further elaboration of these compounds to natural anthracyclines (and analogs) is underway, as well as studies of other more complex dienes.

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References and notes

1 a) - F. Arcamone, Lloydia, 40, 45 (1977); b) - D.W. Henry in "Cancer Chemotherapy" A.C. Sartorelli, Ed., American Chemical Society, Washington, D.C., 1976, Chapter 2.

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6 - This result implies preferential elimination of TMSOH over EtOH after cycloaddition or during work-up.

7 - Cleavage of the aryl ethyl ether ($AlCl_3$, CH_2Cl_2, 20°C) followed by hydrolysis of the enol ether (wet acetone, H^+, reflux).

8 - J.P. Gesson, L. Di Giusto and J.C. Jacquesy, Tetrahedron, 34, 1715 (1978).

9 - All compounds gave satisfactory gave satisfactory analytical and mass spectral data. N.M.R ($CDCl_3$), except for the highly insoluble ketone 9 and I.R (KBr) are given below.
8 : δ 2.57 (t, 2H), 3.23 (t, 2H), 3.67 (s, 2H), 7.18-8.20 (m, 5H), 12.95 (s, 1H, chelated OH); $\nu_{max.}$ 1725, 1665, 1630 cm^{-1}.
9 : $\nu_{max.}$ 1710, 1640, 1610 cm^{-1}.
12: δ 2.58 (t, 2H), 3.22 (t, 2H), 3.67 (s, 2H), 7.18-7.82 (m, 4H), 11.93 (s, 1H, chelated OH), 12.40 (s, 1H, chelated OH); $\nu_{max.}$ 1715, 1670, 1620 cm^{-1}.
14: δ 2.57 (t, 2H), 3.23 (t, 2H), 3.63 (s, 2H), 4.07 (s, 3H), 7.20-7.99 (m, 4H), 13.27 (s, 1H, chelated OH); $\nu_{max.}$ 1710, 1670, 1630 cm^{-1}.
15: δ 2.57 (t, 2H), 3.20 (t, 2H), 3.63 (s, 2H), 4.02 (s, 3H), 7.22-7.97 (m, 4H), 12.73 (s, 1H, chelated OH); $\nu_{max.}$ 1710, 1665, 1625 cm^{-1}.

10 - a)-R.K. Boeckman Jr., T.M. Dolak, K.O. Culos, J. Amer. Chem. Soc., 100, 7098 (1978) and references cited therein.
b)-Ketones 14 and 15 are easily distinguished on T.L.C. plates (Merck : silica gel GF 250 µm) using 5% Et_2O in CH_2Cl_2 as eluent. 14 : R_f = 0.57 and 15 : R_f = 0.43.

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