Tetrahedron Letters,Vol.24,No.27,pp 2757-2760,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

REGIOSPECIFIC SYNTHESIS OF TETRACYCLIC ALKENES PRECURSORS OF VARIOUS ANTHRACYCLINONES

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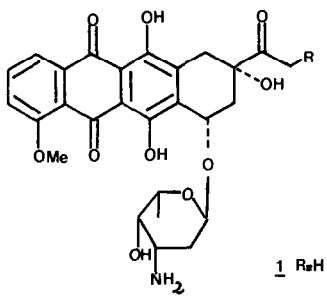
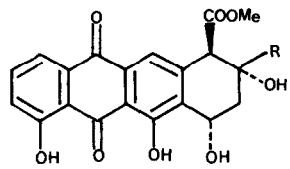
Abstract : The preparation of novel trimethylsilylketene acetals and their cycloaddition with juglone are described, thus constituting a rapid and regiospecific access to key 11-deoxyanthracycline intermediates.

Among naturally occuring anthracyclines daunorubicin 1 and doxorubicin 2 have emerged as efficient, clinically effective anticancer agents[1]. However other compounds devoid of the hydroxy acetyl side chain also exhibit interesting cytotoxic properties. Examination of their structures shows the presence at C9 of alkyl groups (methyl, ethyl...) together with an hydroxyl function. This is especially the case of 11-deoxyanthracyclines whose aglycones are aklavinone 3, auramycinone 4, nogalamycinone 5 or steffimycinone 6[2].



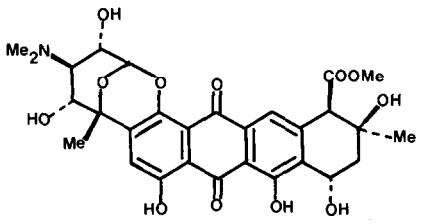
1 R=H

2 R=OH



3 R=Et

4 R=Me



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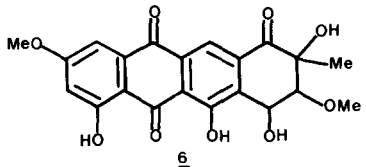

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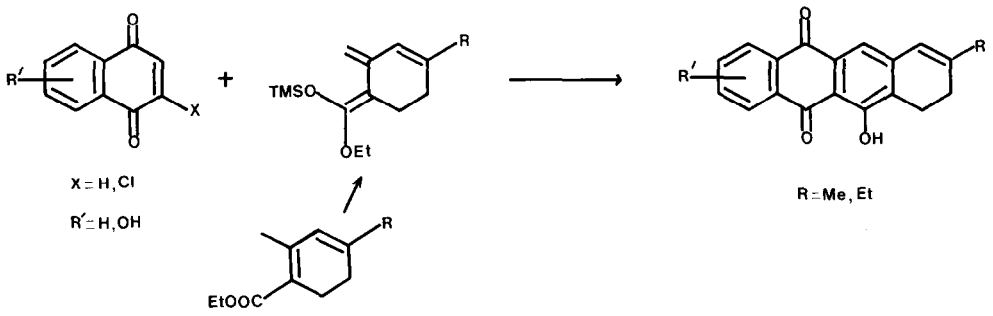
Current interest in the total synthesis of 3[3] leads us to describe here a general strategy toward such anthracyclines using as the key step a Diels-Alder type cycloaddition of trimethyl silyl ketene acetals with naphthoquinones (Scheme), an extension of our previously described route to 11-deoxy[4] or 6-deoxy[5] daunorubicine intermediates.

Scheme

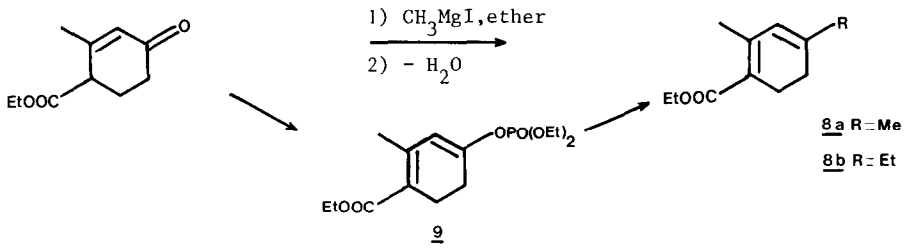


The tetracyclic alkenes thus obtained may be considered as flexible intermediates toward the above compounds and some of them have already been prepared, although by more tedious procedures, and further elaborated, to natural or hemisynthetic anthracyclinones[6a,b].

PREPARATION OF KETENE ACETALS 7a AND 7b

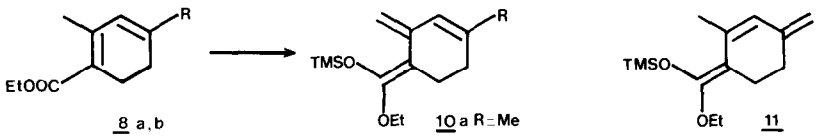
The required synthons 7a and 7b may be a priori obtained by quenching the corresponding dienolates with chlorotrimethylsilane (TMSCl) and so the critical step appears to be the regiospecific deprotonation (at least when R=CH_3) of the dienolates 8a and 8b.

8a is readily avalaible following a slight modification of the procedure of Julia[7] in about 51% yield : addition of CH_3MgI in ether to a solution of Hagemann ester maintened at 0°C followed by thermal or acidocatalyzed dehydration and SiO_2 chromatography. Similar experiments with EtMgBr affords only an untractable mixture of olefins which could not be isomerized cleanly to 8b under various conditions. However treatment of the enol phosphate 9, prepared in quantitative yield from Hagemann ester (1,1 eq. NaH, $(EtO)_2POCl$, ether, 0-20°C) with Me_2CuLi in ether[8] (-78°C to + 20°C) gives 8b[9] (30%) together with some dialkylated derivative.



Deprotonation of 8b under standard conditions[4,5] (1,1 eq. LDA, THF, -78°C, N_2) followed by addition of TMSCl (1,3 eq., - 78°C to + 20°C) gives 10b[10] (90%) as a pale yellow oil readily characterized by ^1H NMR which shows the absence of other isomers.

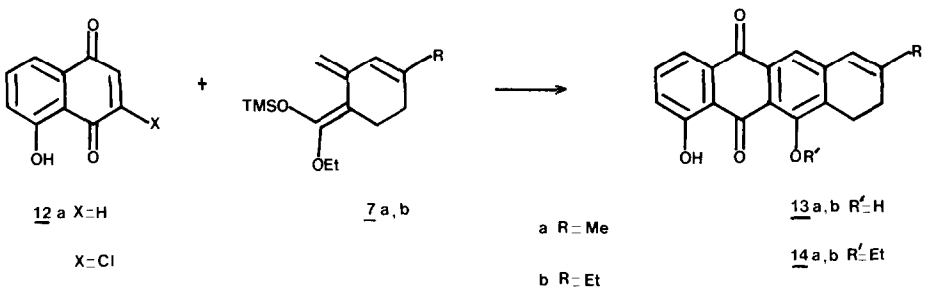
Similarly 8a affords a single ketene acetal whose structure, as judged by ^1H NMR, is consistent with either 10a or 11[10]. Nevertheless cycloaddition with naphthoquinones will



exclude the more conjugated formula 11. It is thus clear that deprotonation occurs on the methyl group closer to the carbonyl function which may be initially complexed by the lithium base.

CYCLOADDITION OF 7a AND 7b

As previously observed for other ketene acetals[4,5] condensation with naphthoquinones proceeds rapidly at 0-20°C in various anhydrous solvents (CH_2Cl_2, THF, Benzene) using only a 1.1 molar excess of either 7a or 7b.



Commercially avalaible juglone 12a combines with 7a to give after work-up under air (oxidation of the intermediate hydroquinone) a 1:4 mixture of phenol 13a and of the corresponding ether 14a which is then treated, without purification, with $AlCl_3$ (10 eq.) in refluxing CH_2Cl_2 overnight. After extraction and rapid column chromatography over SiO_2 (CH_2Cl_2 eluent) 13a, m.p. 174-176°C (m.p. Litt.[14] = 177°C)[11] is isolated in 60% overall yield from 12a. Similar experiments with 7b and 12a affords also a 60% yield of 13b, m.p. 145-147°C (m.p. Litt.[6b] = 147°C)[11].

Under these conditions trace amounts (∿ 6%) of the corresponding fully aromatized tetracyclic compounds are also obtained and care must be taken in the choice of solvents condensation for as well as starting naphthoquinones[12]. However phenol 13a can be obtained directly from the readily avalaible 3-chloro juglone 12b[13] in 55% yield.

The condensation of these novel ketene acetals thus affords a regiospecific, two-steps preparation of key anthracyclinone intermediates from juglone (or other naphthoquinones).

13b has already been converted to (±) decarbomethoxy aklavinone in 3 steps by Kende[6a], and to β_1 citromycinone in 2 steps by Krohn[6b]. Compound 13a has been used in a recently published approach to aranciamycinone[14].

Aknowledgements - We thank the CNRS and Laboratoires HOECHST (Paris) for financial support.

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2 - See ref. 1, Chapter 8, for compounds 3, 5 and 6. See A. Fujiwara, T. Hoshino, M. Tazoe and M. Fujiwara, J. Antibiot., 34, 608 (1981) for 4.

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9 - All new compounds five satisfactory analytical and mass spectral data. Melting points were taken on a Büchi 510 apparatus and are uncorrected. 8b colorless oil; NMR ($CDCl_3$; δ 1.10 (t, 3H), 1.30 (t, 3H), 2.15 (s, 3H), 4.15 (q, 2H), 5.60 (s, W_H 4Hz, 1H).

10 - 10a NMR (CCl_4), δ 0.17 (s, 9H), 1.23 (t, J=7Hz, 3H), 1.70 (s, 3H), 3.77 (q, J=7Hz, 2H), 4.73 (d, J=2Hz, 1H), 5.03 (d, J:2Hz, 1H), 5.65 (s, W_H 4Hz, 1H).
10b NMR (CCl_4), δ 0.17 (s, 9H), 3.77 (q, 2H), 4.74 (d, J:2Hz, 1H), 5.07 (d, J=2Hz, 1H), 5.67 (s, W_H 4Hz, 1H).

11 - 13a NMR ($CDCl_3$), δ 2.00 (s, 1H), 2.40 (t, J=7Hz, 2H), 2.86 (t, J=7Hz, 2H), 6.30 (s, 1H), 7.25-7.74 (complex, 4H), 11.90 (s, 1H), 12.01 (s, 1H). I.R. (CH_2Cl_2) : 1670 (non chelated carbonyl), 1630 (chelated carbonyl). S.M. m/z : 306 (100), 304 (70), 291 (94), 288 (31), 202 (29), 189 (38.4), 153 (35.8), 121 (16.6).
13b NMR ($CDCl_3$), δ 6.20 (s, 1H), 7.10-7.70 (complex, 4H), 12.07 (s, 1H), 12.20 (s, 1H). I.R. (CH_2Cl_2) : 1670 (non chelated carbonyl), 1630 (chelated carbonyl). S.M. m/z : 320 (69), 318 (11), 303 (34.3), 291 (100).

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(Received in France 5 April 1983)