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ANTHRACYCLINES. II - REGIOSPECIFIC SYNTHESIS OF 6-DEOXYANTHRACYCLINE INTERMEDIATES[1]

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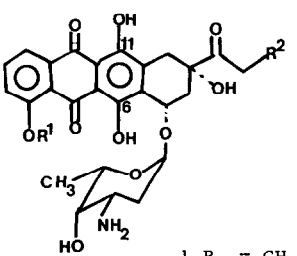
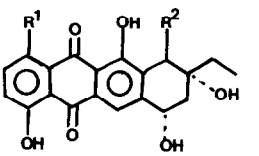
Summary - Reaction of vinyl ketene acetal 4, easily prepared from diethyl 4-oxopimelate, with various naphthoquinones affords a short and regiospecific route to tetracyclic ketones, key intermediates for the further synthesis of 6-deoxyanthracyclines.

Anthracycline antibiotics such as daunorubicin 1, doxorubicin 2 and carminomycin 3 are potent clinical antitumor agents[2]. Numerous analogs with alterated sugar and/or aglycone have already been prepared and have permitted to gain more informations about structure-activity relationship[3]. Modification of the anthraquinone part of these molecules appears to have been less studied due to the lack of efficient regiospecific routes to these tetracyclic compounds. The recent isolation by Arcamone[4] of the cytotoxic 11-deoxy daunorubicin and 11-deoxy doxorubicin demonstrate that two phenolic groups in ring B (at the 6 and 11 position) are not essential for antitumor activity. Furthermore this autor has also shown that the 6-methyl ether of carminomycin is almost as potent as daunorubicin itself against P 388 lymphocytic leukemia in mice[5].

These reasons prompted us to describe some months ago a general and short synthesis of tetracyclic ketones precursors of 11-deoxy anthracyclines. We wish now to disclose a similar approach to the 6-deoxy series based on cycloaddition of vinyl ketene acetal 4 with various naphthoquinones. The tetracyclic ketones thus obtained may also be considered as versatile intermediates for the synthesis of α-citromycinone 5, γ-citromycinone 6 and α_2-rhodomycinone 7, aglycones of anthracycline antibiotics isolated by Brockmann[6].





1 $R_1 = CH_3$, $R_2 = H$

2 $R_1 = CH_3$, $R_2 = OH$

3 $R_1 = R_2 = H$

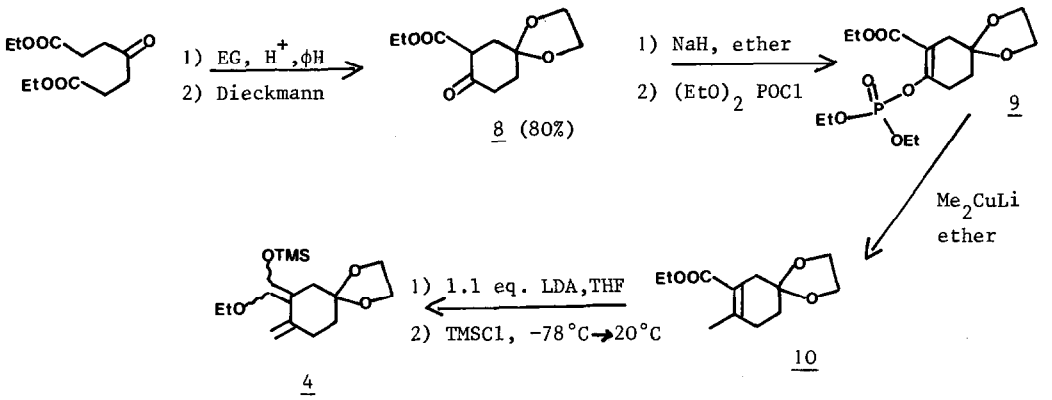
5 $R_1 = H$, $R_2 = OH$

6 $R_1 = R_2 = H$

7 $R_1 = R_2 = OH$

SYNTHESIS OF VINYL KETENE ACETAL 4

8, readily prepared in two steps from commercially avalaible diethyl 4-oxopimelate[7], is converted to 10 by the procedure of Weiler[8] without purification of the intermediate enol phosphate 9 in 60% overall yield. Subsequent treatment of 10 with LDA followed by TMSCl affords 4 as an oil in 91% yield[9]. No trace of the isomeric endocyclic vinyl ketene acetal is observed by NMR thus confirming previous experiments in this laboratory on the deprotonation of alkyl 2-methyl cyclohexene-1 carboxylates[10].



CYCLOADDITION OF 4 WITH NAPHTHOQUINONES

1) - Symmetrical quinones

The reactivity of 4 toward naphthoquinone 11 and naphthazarin 12 was first studied. Initial experiments showed that 4 is less reactive than 15, previously used in our cycloaddition route to 11-deoxyanthracyclines[1], as expected from simple electronic considerations.

Condensations of 4 (1.1 eq.) with 11 and 12 are run in refluxing THF or at room temperature in CH_3CN[11] overnight to yield, in each case after air oxidation, a mixture of ether (R_1 = C_2H_5) and phenol (R_1 = H) in about a 4:1 ratio. Simultaneous cleavage of the ether and ethylene ketal groups to afford 13 (or 14) is best carried out in SbF_5-HF at -40°C[1b]. However these ketones are obtained in similar yield by treatment first with wet acetone containing a few drops of 12N HCl (reflux, 2h) and then with $AlCl_3$ (10 eq.) in dichloromethane (reflux, 16h).

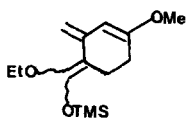
Structures of ketones 13 and 14 are consistent with their spectral data[12]; particularly the UV spectrum of 14 (λ_{max} (MeOH) 520, 508, 488, 477, 465 nm) is similar to the reported spectrum of α_2-rhodomycinone[6] (λ_{max} (cyclohexane) 529, 515, 494, 482 nm) itself characteristic of 1,4,5-trihydroxy anthraquinones.

11 R = H
12 R = OH

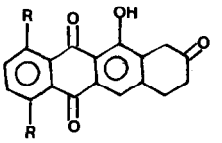
4

(R^1 = H + R^1 = C_2H_5)

SbF_5/HF, -40°C, 10 min.



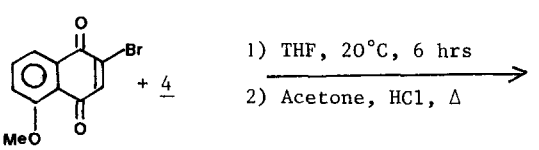
15



13 R = H (57%) m.p. 255°C
14 R = OH (50%) m.p. 268°C

2) - Non symmetrical quinones

Cycloaddition of 4 with 5-methoxy 1,4-naphthoquinone proceeds sluggishly and in low yield. However reaction with the 2-bromo derivative 16[13] occurs rapidly at room temperature in THF to give a single compound after work-up (as judged by TLC) which is readily hydrolyzed (wet acetone, cat. 12N HCl, reflux, 2h) to 17 in 51% overall yield.



16

1) THF, 20°C, 6 hrs
2) Acetone, HCl, Δ

17 R = CH_3 m.p.dec. 262°C
18 R = H m.p. 250°C

The structure proposed for 17 in agreement with its spectral data[14] is confirmed by comparison (NMR, TLC) with an authentic sample prepared by Kende[15] following a totally different route.

Furthermore cleavage of 17 with $AlCl_3$ in CH_2Cl_2 affords the corresponding ketone 18 whose IR and UV spectra are characteristic of a 1,5-dihydroxyanthraquinone[16].

Thus, cycloaddition of 4 with various naphthoquinones appears to be a versatile seven step synthesis of key anthracycline intermediates from diethyl 4-oxopimelate. Further work in this area is currently in progress.

One of us (M.M) thanks the CNRS for financial support.

Notes and references

1a -III[d] International IUPAC symposium on organic synthesis, June 15-20, 1980, Madison, Wisconsin, USA.

b -Anthracyclines I : A general route to 11-deoxyanthracyclines. J.P. GESSON, J.C. JACQUESY and M. MONDON, *Tetrahedron Lett.*, 3351 (1980).

c -A very similar approach has recently been published. J.G. BAUMAN, R.B. BARBER, R.D. GLESS and H. RAPOPORT, *Tetrahedron Lett.*, 4777 (1980).

2 - D.W. HENRY, *Cancer Chemotherapy*, A.C. Sartorelli Ed., American Chemical Society, Washington, D.C, Chapter 2.

3 - F. ARCAMONE, *Lloydia*, 40, 45 (1977).

4 - F. ARCAMONE, G. CASSINELLI, F. DI MATTEO, S. FORENZA, M.C. RIPAMONTI, G. RIVOLA, A. VIGEVANI, J. CLARDY and T. Mc CABE, *J. Amer. Chem. Soc.*, 102, 1462 (1980).

5 - P. MASI, A. SUAROTO, P. GIARDINO, G. IRACI, L. BERNARDI and F. ARCAMONE, *Il Farmaco*, 35, 347, (1980).

6 - H. BROCKMANN and J. NIEMEYER, *Chem. Ber.*, 101, 1341 (1968).

7 - P.D. GARDNER, L. RAND and G.R. HAYNES, *J. Amer. Chem. Soc.*, 78, 3425 (1956).

8 - F.W. SUM and L. WEILER, *Can. J. Chem.*, 57, 1431 (1979).

9 - This unstable oil is used directly in the cycloaddition step without purification.
NMR (CCl_4) : δ 0.20 (s, 9H), 1.23 (t, 3H), 3.80 (q, 2H), 3.90 (s, 4H) and 4.88 (s, 2H).

10- J.P. GESSON, J.C. JACQUESY and M. MONDON, *Tetrahedron Lett.*, 2509 (1980).

11- Y. KITA, J. SEGAWA, J. HARUTA, T. FUJII and Y. TAMURA, *Tetrahedron Lett.*, 3779 (1980).

12- All new compounds give satisfactory analytical and mass spectral data. Melting points were taken on a Kofler block and are uncorrected. Characteristic spectral data are given below :

13 NMR ($CDCl_3$) : δ 2.60 (t, 2H), 3.20 (t, 2H), 3.63 (s, 2H) and 12.87 (s, 1H,chelated OH)
IR (KBr) : λ_{max} 1715, 1665, 1630 cm^{-1}. UV (MeOH) : 208, 230, 246, 262, 330 and 405 nm (shoulder 430 nm).

14 NMR ($CDCl_3$) : δ 2.64 (t, 2H), 3.27 (t, 2H), 3.69 (s, 2H), 12.28 (s, 1H), 12.58 (s, 1H) and 13.04 (s, 1H). IR (KBr) : ν_{max} 1715, 1645, 1610 cm^{-1}. UV (MeOH) : see text.

13- A.H. CARTER, E. RACE and F.M. ROWE, *J. Chem. Soc.*, 236 (1942).

14- 17 NMR ($CDCl_3$) : δ 2.60 (t, 2H), 3.20 (t, 2H), 3.63 (s, 2H), 4.03 (s, 3H) and 12.70 (s, 1H).
IR (KBr) : ν_{max} 1710, 1660, 1625 cm^{-1}. UV (MeOH) : 226, 262, 408 nm.

15 - A.S. KENDE, J.P. GESSON and T.P DEMUTH, submitted to Tetrahedron Letters.

16 - NMR ($CDCl_3$) : δ 2.63 (t, 2H), 3.24 (t, 2H), 3.69 (s, 2H), 12.63 (s, 1H) and 13.00 (s, 1H).
IR (KBr) : ν_{max} 1710, 1630 cm^{-1}. UV (MeOH) : 228, 257, 418 and 436 nm.
α-citromycinone and 1,5-dihydroxy anthraquinone exhibit similar absorption maxima at 418 and 436 nm in cyclohexane. See ref. 6.

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