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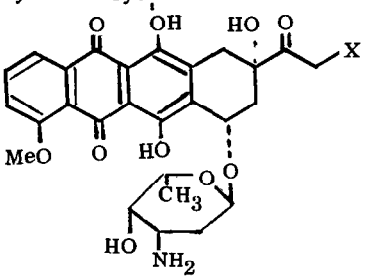
REGIOSPECIFIC SYNTHESIS OF LINEAR QUINONE SYSTEMS. EFFICIENT CONVERGENT SYNTHESIS OF ANTHRACYCLINE INTERMEDIATES[1]

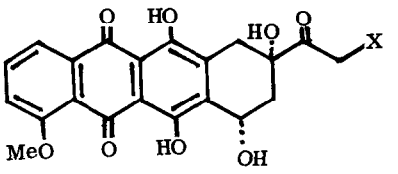
Kathlyn A. Parker* and James L. Kallmerten

Department of Chemistry, Brown University, Providence, Rhode Island 02912

The antineoplastic activity and challenging structural features of the anthracycline antibiotics have caused extensive efforts to be directed toward their chemical synthesis.[2] In particular, Adriamycin (1a) and daunomycin (1b) have become the focus of much attention. Despite many excellent contributions in this area, regiospecific syntheses of the aglycones 2[3] have been reported only recently.[2b,3a,4]

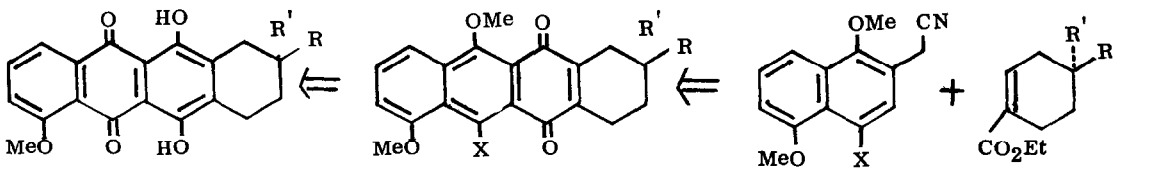


1a X=OH
1b X=H



2a X=OH
2b X=H

In this communication, we are pleased to report the application of our previously proposed[5] regiospecific annelative quinone synthesis[6] (summarized below) to the synthesis of quinone 4a, viewed as a precursor to the known tetracyclic Adriamycin intermediate 3a.[2b,7]



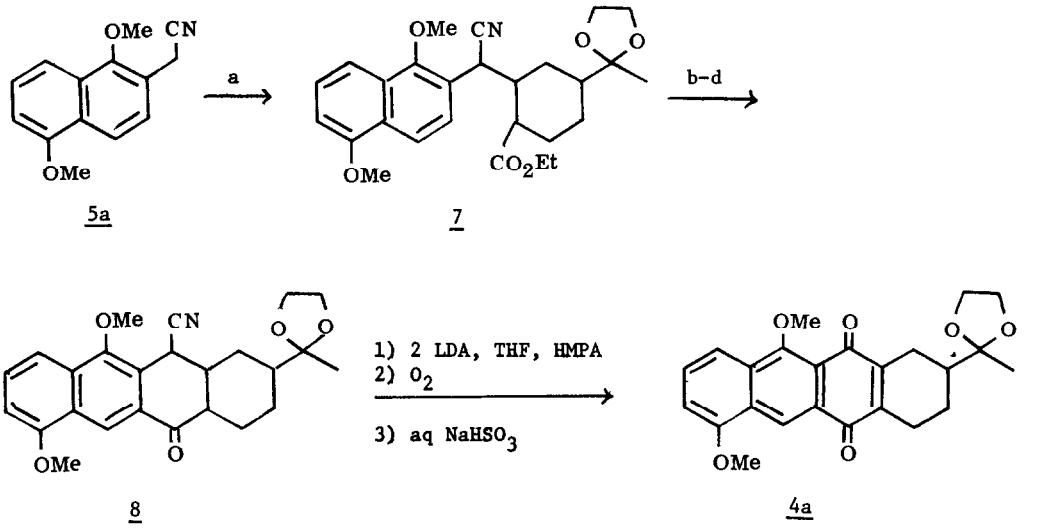
3a R=$COCH_3$, R'=H
3b R, R'=O

4a R=  , R'=H, X=H
4b R, R' = OCH_2CH_2O , X=OMe

5a X=H
5b X=OMe

6a R=  , R'=H
6b R, R'=OCH_2CH_2O

Regiospecific annelation is accomplished as follows. Michael addition[8] of nitrile 5a to ester 6a gave cyanoester 7;[9] basic hydrolysis, intramolecular Friedel-Crafts reaction, and reketalization of the side-chain keto group gave cyanoketone 8. The sequence is completed by a new reaction in which the quinone moiety is elaborated by an oxidative decyanation procedure.[10] Treatment of ketone 8 with two equivalents of LDA followed by oxygen gas and sodium bisulfite work-up gave quinone 4a, mp 114-116°, in 82% yield. This conversion is general for the production of the quinone moiety as part of an extended conjugated system.[11]



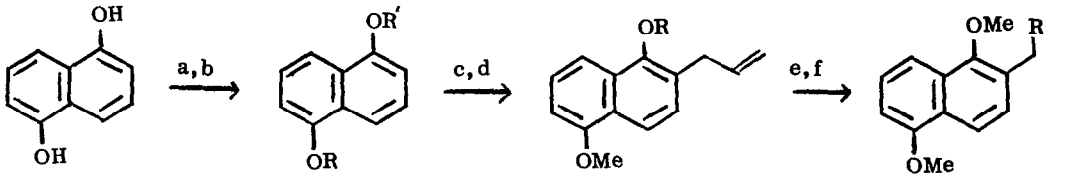
5a 7 8 4a

Scheme 1

a) NaH, -56°; then ester 6a, - 56°, 3 hr; 0°, 3 hr; overnight, room temperature; (77%),[8] mp 75-80°. b) KOH (1.2 equiv), EtOH, H_2O (84%), c) TFA, TFAA (2:3),(81%), mp 221-224°. d) $HOCH_2CH_2OH$, TsOH, $HC(OEt)_3$, room temperature (90%).

This convergent approach is particularly attractive because of the short sequences required for preparation of the key intermediates, nitrile 5a and ester 6a, and the notably low costs of the starting materials, 1,5-naphthalenediol (9) and perillartine (15).

Naphthylacetonitrile 5a was synthesized as shown in Scheme 2. 1,5-Dimethoxy-2-allyl-naphthalene (13) was prepared by the method of Hill et al.[12] in 28% overall yield.[13] Ozonolysis gave the unstable aldehyde 14 which as converted to the desired nitrile 5a by hydroxylamine-O-sulfonic acid. Potentially more efficient methods of converting naphthol 10 to nitrile 5a are being investigated.[14]



9

10 R=Me, R'=H
11 R=Me, R'=$CH_2CH=CH_2$

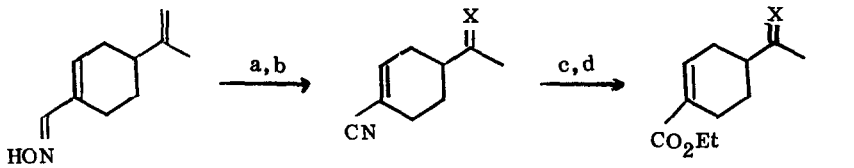
12 R=H
13 R=Me

14 R=CHO
5a R=CN

Scheme 2

a) Me_2SO_4, 2 equiv KOH b) $CH_2=CHCH_2Br$, K_2CO_3, acetone, 24 hr reflux (31% from 9 to 11[13]) c) 200°, 2 hr d) MeI, K_2CO_3, acetone (91% from 11 to 13) e) O_3, CH_2Cl_2/MeOH, 1/1 f) H_2NOSO_3H, MeOH (24% from 13 to 5a, mp 48-51°).

Ester 6a was obtained from perillartine in four steps according to Scheme 3. Dehydration and selective ozonolysis[15] followed by dimethylsulfide reductive work-up gives ketonitrile 17; ethanolysis and ketalization afforded the desired ester 6a.



15

16 X=CH_2
17 X=O

18 X=O
6a X=OCH_2CH_2O

Scheme 3

a) MsCl, pyr (95% yield of 16) b) O_3, MeOH, 1% pyr, then CH_3SCH_3, c) HCl, EtOH (44% from 16 to 18) d) TsOH, $HOCH_2CH_2OH$ (Quantitative)

Efforts to convert quinone 4a to the known Adriamycin intermediate 3a are underway.

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We thank Professor Andrew S. Kende for sending us a copy of his manuscript so that we could submit our results for simultaneous publication.

REFERENCES

1. Portions of this work were reported at the Northeast Regional Meeting of the American Chemical Society, Boston, Massachusetts, June 25-28, 1978.

2. The most recent contributions in this field are listed here. References 2a and 2b include extensive and current bibliographies on anthracyclinones.

a) J. R. Wiseman, N. I. French, R. K. Hallmark, and K. G. Chiong, Tetrahedron Letters, 3765 (1978);
b) J. S. Swenton and P. W. Raynolds, J. Am. Chem. Soc., 100, 6188 (1978);
c) F. A. J. Kerdesky and M. P. Cava, J. Am. Chem. Soc., 100, 3635 (1978).

3. Both dideoxydauomycinone (3a) and ketone 3b have been converted to 7-deoxydauonmycinone, See references 3a-c. 7-Deoxydauomycinone has been converted to daunomycin and Adriamycin; See references 3d and 3e.
a) R. D. Gleim, S. Trenbeath, R. S. D. Mittal and C. J. Sih, Tetrahedron Letters, 3385 (1976). An alternative method has been used in the 4-demethoxy series; F. A. J. Kerdesky and M. P. Cava, J. Am. Chem. Soc., 100, 3635 (1978);
b) A. S. Kende, Y. Tsay, and J. E. Mills, J. Am. Chem. Soc., 98, 1967 (1976);
c) T. H. Smith, A. N. Fujiwara, W. W. Lee, H. Y. Wu, and D. W. Henry, J. Org. Chem., 42, 3653 (1977) and references therein;
d) E. M. Acton, A. N. Fujiwara and D. W. Henry, J. Med. Chem., 17, 659 (1974);
e) W. Barbieri, G. Franceschi, and S. Penco, Chem. Ind. (Milan), 51, 834 (1969).

4. A regiospecific Diels-Alder approach has been reported by T. R. Kelly, G. W. Gillard, R. N. Goerner, Jr., J. M. Lyding, J. Am. Chem. Soc., 99, 5513 (1977).

5. K. A. Parker and J. L. Kallmerten, Tetrahedron Letters, 4557 (1977).

6. Conceptually similar approaches to linear quinone systems have recently been reported: F. M. Hauser and R. P. Rhee, J. Org. Chem., 43, 178 (1978) and G. A. Kraus and H. Sugimoto, Tetrahedron Letters, 2263 (1978).

7. A regiospecific synthesis of 3b by this same approach from nitrile 5b and ester 6b has been completed; see accompanying communication, A. S. Kende, J. Rizzi, and J. Riemer, Tetrahedron Letters, 0000 (1979).

8. We thank Professor Andrew S. Kende for suggesting this modification of experimental conditions. Yields are generally higher in our hands with NaH than with LDA.

9. All new compounds cited in this communication had infrared and nmr spectra which were in accord with the assigned structures.

10. Oxidative decyanation of simple nitriles to give ketones has been studied. See S. J. Selikson and D. S. Watt, J. Org. Chem., 40, 267 (1975).

11. a) The details of several examples of this reaction will be reported in a full paper. b) In the case of 4-cyano-3-cyclohexenone, however, simple aromatization is observed; p-cyanophenol is isolated in 42% yield. This product is invariably accompanied by starting cyanoketone. c) 5,10-Anthraquinones have been prepared from 10-cyano-5-anthrols with alkaline hydrogen peroxide. See The Chemistry of the Quinonoid Compounds, Part 1, S. Patai, ed., New York, John Wiley & Sons, 1974, p. 139.

12. P. Hill, W. F. Short, and H. Stromberg, J. Chem. Soc., 1937, 937.

13. The low-yield step in this sequence (9 → 13) is the monomethylation of diol 9 according to O. Fischer and C. Bauer, J. Prakt. Chem., 94, 13 (1916). We have been unable to improve the yield of monomethylated product by varying conditions. The use of Moore's procedure[16] for preparation of naphthol 10 (diol 9 + 2 eq. CH_3I, then 1 eq EtSNa) increases the overall yield of the sequence 9 → 13 to 61%. In our hands, the older procedure is more convenient however, despite the lower yield.

14. K. A. Parker, S.-K. Kang, and T. Iqbal, work in progress.

15. G. Slomp, Jr., and J. L. Johnson, J. Am. Chem. Soc., 80, 915 (1958).

16. D. Rutoloto, S. Lee, R. Sheldon, and H. Moore, J. Org. Chem., 43, 2305 (1978), footnote 10.

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