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THE SYNTHESIS OF 4-DEMETHOXYDAUNOMYCIN

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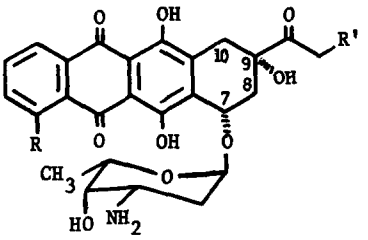
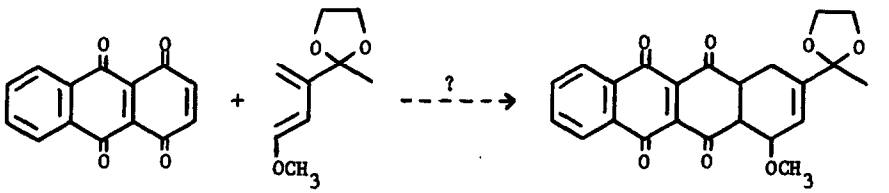
In the past decade the anthracyclines adriamycin (1), daunomycin (2) and carminomycin (3) have come to be recognized as being among the most effective drugs available for the treatment of a broad spectrum of human cancers. More recently, 4-demethoxydaunomycin (4) has been shown



1, R = OCH_3, R' = OH
2, R = OCH_3, R' = H
3, R = OH, R' = H
4, R = R' = H

to exhibit even greater activity than 1.[2] We now report a synthesis of this compound.[3]

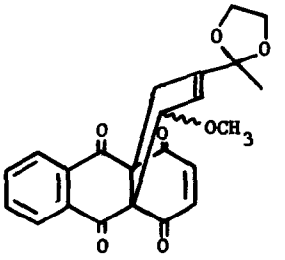
As part of a program directed toward the development of effective routes to the anthracyclines,[4] we had occasion to examine the feasibility of an approach which embodied, as the key constructive step, the Diels Alder reaction between 5[5] and 6 (Eq. 1).[6,7] Distressingly, this



(Eq. 1)

5 6 7

putative route to 7 fails utterly, due to the obtrusion of the alternative cycloaddition pathway which affords the "internal" adduct 8 in >80% isolated yield. This finding initially



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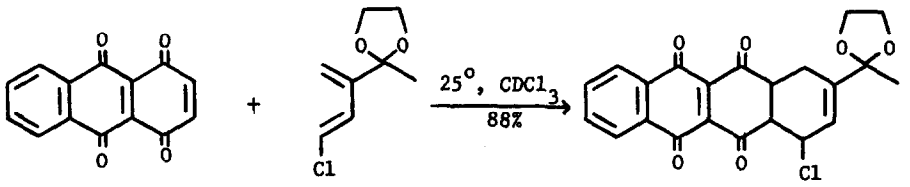
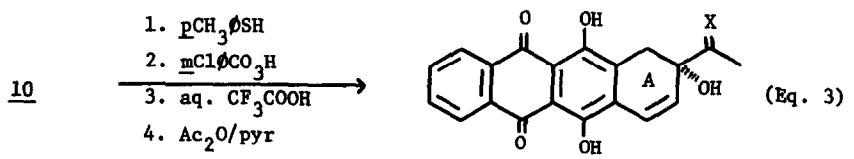
provided a less than welcome incentive to explore alternate approaches to the anthracyclines, but further investigation afforded a less drastic solution. In particular, the simple expedient[8] of replacing methoxydiene 6 with chlorodiene 9 overcomes the disastrous outcome of the original cycloaddition with 5 and gives the desired adduct 10 in 88% yield (Eq. 2).



5 9 10 (Eq. 2)

Adduct 10 can be converted to 11 in four steps (40% overall yield from 5) using the sequence indicated in Equation 3; omission of the ketal hydrolysis step (aq. CF_3COOH) gives 12 in 51% overall yield from 5.

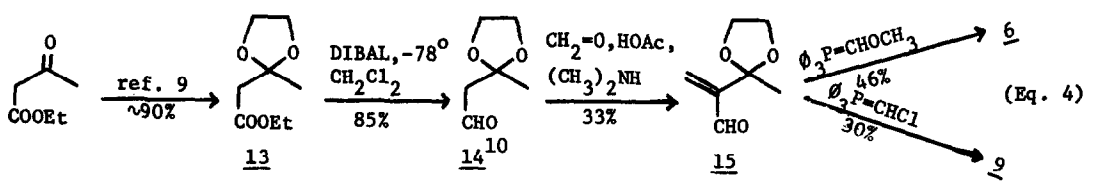


(Eq. 3)

11, X = O

12, X = $-OCH_2CH_2O-$

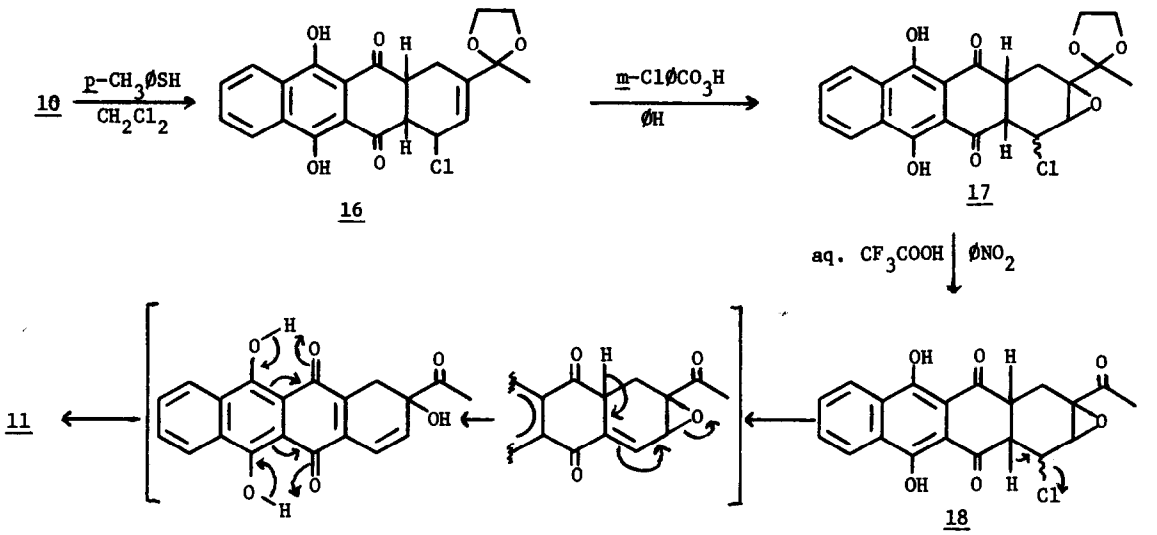
Multigram quantities of dienes 6 and 9 are available in four steps from acetoacetic ester using the incompletely optimized sequences shown in Equation 4.[10]



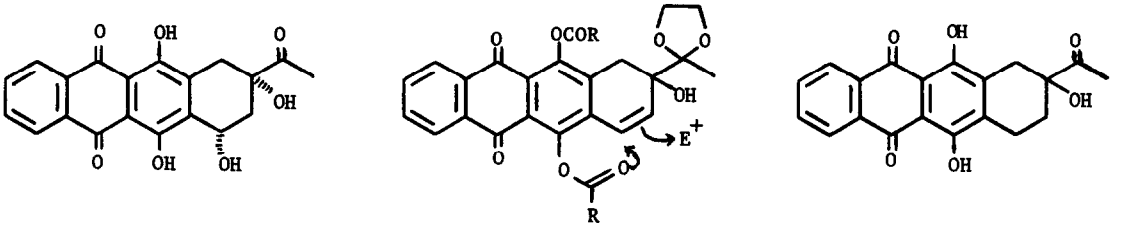
13 14 15 6 9 (Eq. 4)

Consideration of the reagents employed in Eq. 3 might suggest that the development of the A-ring functionality proceeds via a 1,3-allylic sulfoxide transposition. In fact, however, characterization of intermediates 16, 17 and 18 reveals the incursion of an entirely different pathway (Scheme 1).

Scheme 1



With 11 and 12 in hand, conversion of these compounds to 4-demethoxydaunomycinone (19) would appear trivial. But innumerable attempts [CF_3COOH, $Hg(OCOCF_3)_2$, HX, AcOH/hν, hydrozirconation, HOX, $ØSeO_2CR$, etc., as well as the generalized approach suggested by 20] to achieve this seemingly straightforward transformation so far have been completely unavailing (in most cases A-ring aromatization is the principle mode of reaction observed).



In view of these difficulties, confirmation of the structure of 11 was sought. This was achieved by reduction (H_2, Pd/C, EtOH, 1 atm) of 11 to (±)-21. The (±)-21 so obtained (mp 193-95°)[11] is identical (except for chirality-dependent properties) to an authentic sample of (S)-21 provided by Dr. F. Arcamone.[2,11] The obtention of 21 thus affirms the structure assigned to 11; it also constitutes a formal total synthesis of 4-demethoxydaunomycin (4).[2,3b] Efforts to achieve the 11/12 → 19 transformation continue.[12]

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References and Notes

1. Recipient of NIH Research Career Development Award (CA-00040), 1975-80.
2. F. Arcamone, L. Bernardi, P. Giardino, B. Patelli, A. DiMarco, A.M. Casazza, G. Pratesi and P. Reggiani, Cancer Treatment Rep., 60, 829 (1976) and F. Arcamone, Lloydia, 40, 45 (1977).
3. For other syntheses of 4 and/or its aglycone see a) C.M. Wong, D. Popien, R. Schwenk and J. Te Raa, Can. J. Chem., 49, 2712 (1971); b) A.S. Kende, D.P. Curran, Y. Tsay and J.E. Mills, Tetrahedron Lett., 3537 (1977); c) F.A.J. Kerdesky and M.P. Cava, J. Am. Chem. Soc., 100, 3635 (1978) and ref 2. See also F. Suzuki, R.D. Gleim, S. Trenbeath and C.J. Sih, Tetrahedron Lett., 2303 (1977).
4. For related studies from this laboratory see a) T.R. Kelly, R.N. Goerner, Jr., J.W. Gillard and B.K. Prazak, Tetrahedron Lett., 3869 (1976); b) T.R. Kelly, J.W. Gillard and R.N. Goerner, Jr., ibid, 3873 (1976); c) T.R. Kelly, J.W. Gillard, R.N. Goerner, Jr., and J.M. Lyding, J. Am. Chem. Soc., 99, 5513 (1977); d) T.R. Kelly, Tetrahedron Lett., 1387 (1978).
5. L.F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. 1, Wiley, New York, 1967; p. 538.
6. For related studies on the Diels Alder reactions of quinizarinquinones (e.g., 5) see H.H. Inhoffen, H. Muxfeldt, V. Koppi and J. Heimann-Trosien, Ber., 90, 1448 (1957); W.W. Lee, A.P. Martinez, T.H. Smith and D.W. Henry, J. Org. Chem., 41, 2296 (1976); A.M. Birch, A.J.H. Mercer, A.M. Chippendale, and K.W. Greenhalgh, J.C.S. Chem. Comm., 745 (1977) and ref. 4a. See also J. Altman, E. Cohen, T. Maymon, J.B. Petersen, N. Reshef and D. Ginsburg, Tetrahedron, 25, 5115 (1969).
7. For the use of the 5-methoxy derivative of 5 in the synthesis of daunomycinone see: A.S. Kende, Y.-G. Tsay and J.E. Mills, J. Am. Chem. Soc., 98, 1967 (1976).
8. That the substitution of 9 for 6 might lead to the desired terminal adduct (10) was suggested by the observations of Kende et al.[7] and ourselves.[4a] Specifically, we envisaged that replacement of 6 with the less electron-rich diene 9 might afford the desired external[4a] adduct 10.
9. Cf. E.J. Salmi, Ber., 71B, 1803 (1938).
10. The reduction of 13 to 14 is routinely conducted on a 100g scale. For an alternative synthesis of 14 see T. Oishi, M. Nagai and Y. Ban, Tetrahedron Lett., 491 (1968).
11. Racemic 21 has also been prepared by Kende et al.[3b] who reported that its mp is 160-62°. The difference in the melting points observed by Kende et al. and ourselves is presumably due to polymorphism. The nmr spectrum of "our" 21 is superimposable on that of the (S)-21 provided by Dr. Arcamone (both spectra recorded on our instrument) and identical to that reported for (±)-21 by Kende et al.[3b] except that the two proton singlet for the peri OH's which Kende et al. report[3b] appears at δ 13.54 occurs at δ 13.32 on our instrument [for both "our" 21 and the (S)-21].
12. Melting points or boiling points (uncorrected) and 60 MHz spectra (in $CDCl_3$/TMS, only distinctive peaks are given) for all new compounds are: 6: bp ∿55° (.3 mm), δ 1.50 (3H, s, CH_3), 3.60 (3H, s, OCH_3), 3.95 (4H, m, $-OCH_2CH_2O-$), 5.00 (1H, br s, $C=CH_b-H_a$), 5.09 (1H, d, J∿2Hz, $C=CH_a-H_b$), 5.42 (1H, d, J=12Hz, $CH_3OCH=CH-$), 6.94 (1H, d, J=12Hz, $CH_3OCH=$). 8: mp 218-20°, δ 1.50 (3H, s, CH_3), 1.95 (1H, br d, J=19Hz, $>CH_b-H_a$), 3.21 (3H, s, OCH_3), 3.28 (1H, d, J=19Hz, $>CH_a-H_b$), 3.9 (4H, m, $-OCH_2CH_2O-$), 4.77 (1H, d, J=5Hz, $CHOCH_3$), 6.30 (1H, m, $-CH(OCH_3)CH=C$), 6.56, 6.73, 6.97, 7.14 (2H, ABq, $-COCH=CHCO-$), 7.95 (4H, m, Ar-H). 9 bp 80° (17 mm, Kugelrohr), δ 1.52 (3H, s, CH_3), 3.88 (4H, m, $-OCH_2CH_2O-$), 5.15 (1H, br s, $C=CH_b-H_a$), 5.38 (1H, d, J∿2Hz, $C=CH_a-H_b$), 6.28, 6.51, 6.58, 6.81 (2H, ABq, $ClCH=CH-$). 10: mp 254-5° (starts to turn red at ∿130°), δ 1.55 (3H, s, CH_3), 3.98 (4H, br s, $-OCH_2CH_2O-$), 4.94 (1H, br t, J∿5Hz, C-7 H), 6.10 (1H, br d, J∿5Hz, C-8 H), 7.9 (4H, m, Ar-H). 11: mp 230-33° (insufficiently soluble for useful NMR spectrum). 12: mp 208-10°, δ 1.40 (3H, s, CH_3), 2.92, 3.22, 3.29, 3.59 (2H, ABq, C-10 H's), 4.07 (4H, s, $-OCH_2CH_2O-$), 6.26, 6.41, 7.07, 7.22 (2H, ABq, C-7, C-8 H's), 7.78 (2H, m, Ar-H), 8.30 (2H, m, Ar-H), 13.27 (1H, s, ArOH), 13.37 (1H, s, ArOH). 14: bp 70-73° (16 mm) [lit.[10] 68-69.5 (11 mm)], δ 1.40 (3H, s, CH_3), 2.67 (2H, d, J=3Hz, CH_2CHO), 3.99 (4H, s, $-OCH_2CH_2O-$), 9.75 (1H, t, J=3Hz, $-CHO$). 15: bp 93° (15 mm), δ 1.57 (3H, s, CH_3), 3.91 (4H, m, $-OCH_2CH_2O-$), 6.12 (1H, d, J=1Hz, $C=CH_bH_a$), 6.51 (1H, d, J=1Hz, $C=CH_a-H_b$), 9.65 (1H, s, $-CHO$). 16: mp 184-88°, δ 1.60 (3H, s, CH_3), 3.97 (4H, m, $-OCH_2CH_2O-$), 4.95 (1H, m, C-7 H), 6.19 (1H, m, C-8 H), 7.77 (2H, m, Ar-H), 8.58 (2H, m, Ar-H), 12.98 (1H, s, ArOH), 13.67 (1H, s, ArOH). 17: mp 218-20°, δ 1.55 (3H, s, CH_3), 3.99 (4H, s, $-OCH_2CH_2O-$), 4.79 (1H, ∿t, J∿3Hz, C-7 H), 7.75 (2H, m, Ar-H), 8.45 (2H, m, Ar-H), 13.07 (1H, s, ArOH), 13.75 (1H, s, ArOH). 18: mp 225-8° (starts to turn red ∿130°), δ (CF_3COOH/TMS) 2.44 (3H, s, $COCH_3$), 3.97 (∿3H, m), 5.06 (1H, m, C-7 H), 7.96 (2H, m, Ar-H), 8.61 (2H, m, Ar-H).

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