Tetrahedron Letters No. 37, pp 3403 - 3406.
0040-4039/78/0908-3403$02.00/0
© Pergamon Press Ltd. 1978. Printed in Great Britain.

A SHORT, EFFICIENT SYNTHESIS OF AN ANTHRACYCLINE ANTITUMOR ANTIBIOTIC SYNTHON

Jose Alexander and L.A. Mitscher*
Department of Medicinal Chemistry, The University of Kansas
Lawrence, Kansas, 66045, U.S.A.

Synthetic approaches to the anthracyclines related to adriamycin-daunomycin are of great interest because of the relative costliness of the agents and their useful clinical properties against a relatively broad spectrum of tumors.[1] Of the presently available syntheses, those based upon the Diels-Alder pathways of Kende et al.[2] are preferred because of their efficiency for symmetrically substituted analogs. Some complications inherent in these processes are their relative lack of regioselectivity.[3-9] We report here some of our experiments in which we start with very inexpensive materials and proceed in a few efficient steps to tetracyclic ketones suitable for further elaboration to, for example, 4-demethoxyadriamycin, a highly active analog of the natural antibiotics.[10]

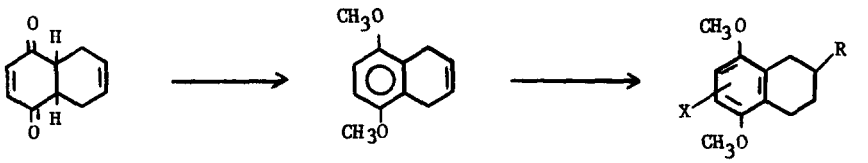
The well-known Diels-Alder adduct (1)[11] of p-benzoquinone and butadiene was converted to dihydronaphthalene ether 2 in 96% yield by refluxing 18 hr. in acetone with Me_2SO_4 and K_2CO_3 [mp. 50°;[12] pmr ($CDCl_3$) 3.25δ (4H, s), 3.76 (6H, s, OCH_3), 5.83 (2H, s) and 6.60 (2H, s)]. Hydroboration with diborane in THF followed by alkaline peroxide oxidation produced alcohol 3 in quantitative yield [mp. 130-131.5; ir(nujol) 3360-3280 cm^{-1}, etc.; pmr ($CDCl_3$) 1.6-2.1δ (3H, m), 2.2-3.2 (4H, m, benzylic CH_2), 3.56 (6H, s, OCH_3), 3.8-4.3 (1H, m, CHOH) and 6.60 (2H, s, ArH)]. Oxidation with pyridinium chlorochromate in CH_2Cl_2 at

room temperature produced, after florisil filtration, 67.5% of known tetralone 4 (mp. 98-99.5).[13] This procedure is a more convenient method of preparation for tetralone 4 than that presently in the literature.[14]

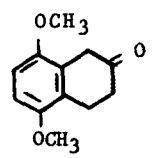
Alcohol 3 was suspended in CH_2Cl_2 at -20° and $BF_3 \cdot Et_2O$ and 100% H_3PO_4 were added. Condensed isobutylene was introduced and the reaction mixture was shaken at room temperature. This produced tert-butylether 5 in 93% yield [syrup, pmr ($CDCl_3$); 1.21δ (9H, s, $(CH_3)_3C$), etc.]. The ether was dissolved in $CHCl_3/CH_3CONH_2$, cooled in ice and brominated with $Br_2/CHCl_3$. After filtration through alumina in hexane, evaporation produced bromo compounds 6 in 94% yield [oil; m/e 344 + 342, etc.; pmr ($CDCl_3$) 1.23δ (9H, s), 1.6-3.3 (7H, m), 3.75 (6H, s) and 6.77 (1H, s, ArH)]. This mixture could be separated by chromatography but for present purposes can be used as such to react with symmetrical esters. It was accordingly cooled to -100° in dry THF and 1.1 molar equivalents of n-BuLi were added. After warming to -80°, 1.1 meq of dimethylphthalate in dry THF was added during 0.5 h. After stirring and allowing to come to room temperature overnight, HOAc was added and the solvents removed. SiGel chromatography produced 65.2% of pure esters 7 for characterization. It was not routinely necessary to purify in this way as solvent washing produced material sufficiently pure for the next step [oil; m/e 426; ir (nujol) 1730, 1610, 1595; pmr ($CDCl_3$) 3.26δ (3H, s, CO_2CH_3), 3.65 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 6.95 (1H, s, ArH), 7.36 (4H, apparent quartet, ArH)]. Cyclization and deblocking was accomplished by dissolving in CH_2Cl_2 and passing in an excess of BCl_3 gas and stirring at room temperature for ca. 48 hr. The reaction mixture was evaporated, triturated with 0.5N HCl and filtered to give cyclized alcohol 8 as a red solid in 96% yield [mp >300°; m/e 310 (M^+), 292, 291, 290; ir (KBr) 3420, 1618, 1580, 1395 and 1245 cm^{-1}; uv (EtOH) 513 nm (ε 4800), 482 (7000), 456 (6090), 326 (2440), 287 (6370), 256 (28000) and 252 (28500); pmr (CF_3CO_2H) 2-3.3δ (6H, m), 5.75 (1H, m), 7.92 (2H, m) and 8.40 (2H, m)]. When cyclized with BBr_3, the reaction was complete in 16 h. but the product contained approximately 50% of the corresponding bromide (9) which could easily be separated by solvent treatments. Oxidation of alcohol 8 to the

corresponding ketone has been reported to proceed in 83% yield.[3] Thus, we have succeeded in devising a short and efficient process from easily accessible materials for compounds well known to be useful for synthesis of antitumor anthracyclines.[2,15] Our present efforts deal with use of this sequence to prepare more highly functionalized synthons.

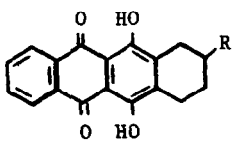
Acknowledgment. We are grateful to ADRIA Laboratories for partial financial support of this work and to Dr. H.J. Eichel for encouragement.



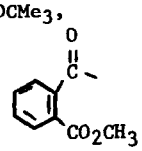
(1)



(4)



(8) R=OH
(9) R=Br

(3) R=OH, X=H
(5) R=$OCMe_3$, X=H
(6) R=$OCMe_3$, X=Br
(7) R=$OCMe_3$,
X= 

REFERENCES AND NOTES

1. F. Arcamone, The Journal of Natural Products, 40, 45 (1977).
2. A.S. Kende, Y. Tsay and J.E. Mills, J. Am. Chem. Soc., 98, 1967 (1976).
3. W.W. Lee, A.P. Martinez, T.H. Smith and D.W. Henry, J. Org. Chem., 41, 2296 (1976).
4. T.R. Kelly, J.W. Gillard and R.N. Goerner, Jr., Tetrahedron Letters, 3873 (1976).
5. T.R. Kelly, R.N. Goerner, Jr., J.W. Gillard and Barbara K. Prazak, ibid., 3869 (1976).
6. M.E. Jung and J.A. Lowe, J. Org. Chem., 42, 2371 (1977).
7. T.R. Kelly, J.W. Gillard, R.N. Goerner, Jr. and J.M. Lyding, J. Am. Chem. Soc., 99, 5513 (1977).

8. A.M. Birch, A.J.H. Mercer, A.M. Chippendale and C.W. Greenhalgh, J. Chem. Soc., Chem. Commun., 745 (1977).

9. A.S. Kende, D.P. Curran, Y. Tsay and J.E. Mills, Tetrahedron Letters, 3537 (1977).

10. F. Arcamone, L. Bernardi, P. Giardino, B. Patelli, A. DiMarco, A.M. Casazza, G. Pratesi and P. Reggiani, Cancer Treatment Reports, 60, 829 (1976).

11. O. Diels and K. Alder, Chem. Ber., 62, 2337 (1929).

12. A.P. Tarentev and P.P. Shavolova, J. Gen. Chem. (U.S.S.R.), 15, 142 (1945).

13. T.R. Lewis, W.B. Dickinson and S. Archer, J. Am. Chem. Soc., 74, 5321 (1952).

14. M.E. Jung and C.A. McCombs, Tetrahedron Letters, 2935 (1970).

15. A.S. Kende and Y.-G. Tsay, J. Chem. Soc., Chem. Commun., 140 (1977).

(Received in USA 5 June1978; received in UK for publication 7 July 1978)