Tetrahedron Letters Vol. 22, pp 397 - 400 0040-4039/81/0129-0397$02.00/0

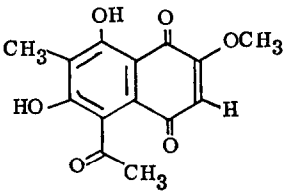
SYNTHESIS OF ANSAMYCINS: AN APPROACH TO THE NAPHTHOQUINONE PORTION OF THE RIFAMYCINS AND STREPTOVARICINS

Kathlyn A. Parker* and Joseph J. Petraitis

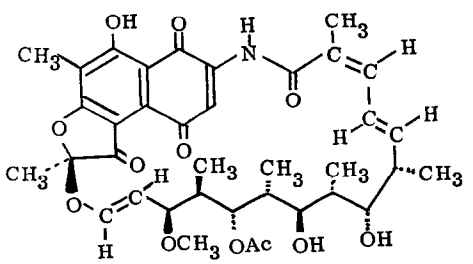
Department of Chemistry, Brown University, Providence, Rhode Island 02912

Naphthoquinone 1, a fully functionalized model for intermediates in ansamycin synthesis, was prepared by the intramolecular Claisen condensation of benzofuran 9 followed by oxidation of the novel tricyclic compound 10.

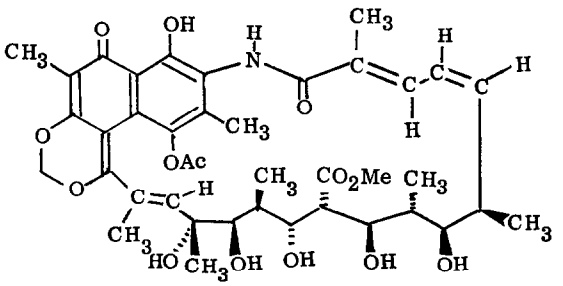
The ansamycins, antibiotics containing an "ansa" chain connecting two nonadjacent carbons of an aromatic nucleus, are of interest because of their unusual macrocyclic structures as well as because of their notable biological activities.[1] Of the ansamycins which contain a naphthalene moiety,[2] the rifamycins and the streptovaricins and their derivatives have received intense study.[1a] Methods designed for the total synthesis of these antibiotics have been confined to the preparation of the stereochemically complex ansa bridge of Rifamycin S [3a-c] and to closure of the macrocycle.[3d] We are pleased to report here the efficient synthesis of the highly substituted naphthoquinone 1, a model for the naphthoquinone portion of the rifamycins and streptovaricins.



1

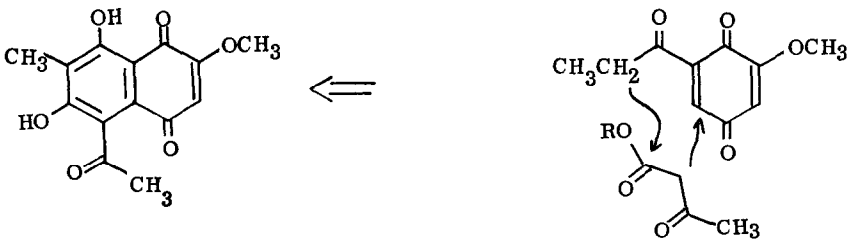


Rifamycin S



Streptovaricin C

Consideration of the pattern of functionality in the target compound 1 led to a retrosynthetic analysis in which the key carbon-carbon bond-forming reactions involve (1) nucleophilic addition of a β-keto ester to an acyl-substituted quinone[4] and (2) intramolecular Claisen condensation involving the acyl substituent and the ester group followed by enolization and oxidation.

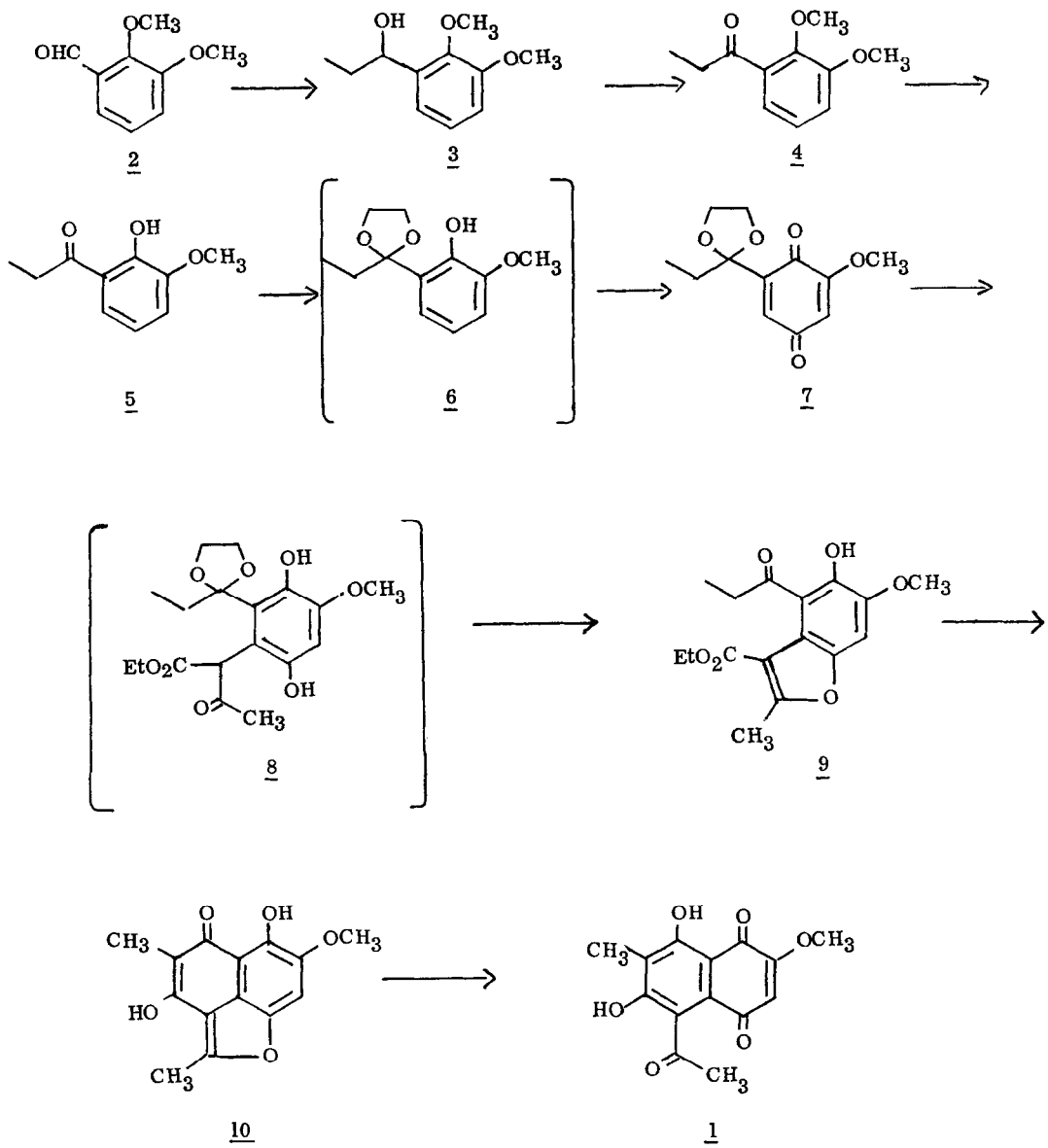


A practical synthesis based on this analysis is shown in Scheme I. 2,3-Dimethoxybenzaldehyde (2) was converted to alcohol 3[5] by ethylmagnesium bromide in 93% yield. Jones oxidation of alcohol 3 proceeded in 86% yield to give ketone 4.[6] Ketone 4 was demethylated by aluminum chloride (3 hrs, 0°) to afford phenol 5, mp 72-73° (lit[7] 73-74°), in 75% yield.

Phenol 5 was conveniently converted to quinone 7, an equivalent of an acyl quinone, in two steps. Ketalization of 5 with ethylene glycol, triethyl orthoformate and p-toluenesulfonic acid in ethanol at reflux was complete in 2 hours. The reaction was quenched by the addition of solid sodium hydroxide. The reaction mixture was concentrated and partitioned between ether and water. The sensitive ketal 6 was isolated by concentration of the ether solution and immediately dissolved in DMF. A catalytic amount of salcomine[8] was added and oxygen was bubbled through the solution for 20 hours. Standard workup and crystallization from hexane afforded benzoquinone 7,[5] mp 88-91°, in 57% yield.

The Michael addition of ethyl acetoacetate to quinone 7 proceeded in ethanol in the presence of 0.1 equivalents of sodium ethoxide. After stirring at room temperature for 1/2 hour, the reaction was terminated by the addition of 6 N HCl which effected deketalization and dehydration of the adduct. Benzofuran 9[5] was isolated in 37% yield (mp 97-99° from ether); ir ($CDCl_3$) 3580, 1725 and 1610 cm^{-1}; nmr ($CDCl_3$) δ=1.22 (t, J=7Hz, 3H), 1.34 (t, J=7Hz, 3H), 2.67 (s, 3H), 2.89 (q, J=7Hz, 2H), 3.93 (s, 3H), 4.35 (q, J=7Hz, 2H), 6.8 (broad s, 1H), 7.01 (s, 1H).

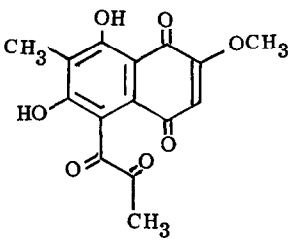
The second key carbon-carbon bond-forming reaction, intramolecular Claisen condensation, was effected when benzofuran 9 was stirred with 6 equivalents of sodium ethoxide in ethanol (2 hr, reflux) to give the novel tricyclic compound 10[5] in 90% yield (mp 235-246° d, from acetone); ir (KBr) 3570, 3460, 1675 and 1605 cm^{-1}; nmr (d_6-DMSO) δ=1.98 (s, 3H), 2.76 (s, 3H), 3.87 (s, 3H), 7.56 (s, 1H), 8.30-11.70 (very broad absorption, 2H); mass spectrum m/e (M^+) 260.



Scheme I

Oxidative cleavage of the hydroquinone monoether moiety of 10 was effected by ceric ammonium nitrate[9] (2 equivalents in 1:1 water:acetonitrile, reflux, 30 min). The target naphthoquinone 1,[5] (mp 222-232° from acetone/hexane) was obtained in 84% yield; ir (KBr) 1625 (broad) and 1240 cm^{-1}; nmr ($CDCl_3$): δ=2.21 (s, 3H), 2.40 (s, 3H), 3.93 (s, 3H), 6.09 (s, 1H), 9.04 (s, 1H) and 12.48 (s, 1H); uv (0.01 N HCl in ethanol): λmax (log ε) = 218 (5.08), 262 (4.93), 300 (4.77), 425 (4.23). The spectra of quinone 1 are very similar to those reported for quinone 11,[10] a degrada-

tion product of Rifamycin S.



11

Acknowledgement: This work was supported by the National Cancer Institute, Department of Health, Education, and Welfare (Grant No. CA 16524). K.A.P. acknowledges additional support in the form of an Alfred P. Sloan Foundation Fellowship and a Camille and Henry Dreyfus Teacher-Scholar Grant.

References

1. Recent reviews include:
   a) K. L. Rinehart, Jr. and L. S. Shield, Fortschr. Chem. Org. Naturst., 33, 231-307 (1976).
   b) K. L. Rinehart, Jr., Accts. Chem. Res., 5, 57-64 (1972).
   c) W. Wehrli, Top. Curr. Chem., 72, 21-49 (1977).

2. More Recent literature includes:
   a) a revision of the structure of naphthomycin: P. V. Deshmukh, K. Kakinuma, J. J. Ameel, K. L. Rinehart, Jr., P. F. Wiley and L. H. Li, J. Am. Chem. Soc., 98, 870 (1976).
   b) structural studies on rifamycin R: E. Martinelli, P. Antonini, R. Cricchio, C. Lancini, and R. J. White, J. Antibiotics, 31, 949 (1978).
   c) structural studies on rubradirins A and B: H. Hoeksema, C. Chidester, S. A. Mizsak, and L. Baczynskyj, J. Antibiotics, 31, 1067 (1978).

3. a) P. A. Bartlett and J. Myerson, J. Am. Chem. Soc., 100, 3950 (1978).
   b) J. Corey and T. Hase, Tetrahedron Letters, 335 (1979).
   c) E. J. Corey and G. Schmidt, Tetrahedron Letters, 2317 (1979).
   *d) E. J. Corey and D. A. Clark, Tetrahedron Letters, 2045 (1980).

4. S. E. Fumagalli and C. H. Eugster, Helv. Chim. Acta, 54, 959 (1971).

5. Infrared and nmr spectra were in accord with the assigned structure. The mass spectrum contained a molecular ion of the appropriate molecular weight and a satisfactory elemental analysis was obtained. *The structure of benzofuran 9 was confirmed by x-ray crystallography.

6. P. Da Re and L. Cimatoribus, Annali di Chimica, 52, 506 (1962).

7. H. Richtzenhain, Chem. Ber., 77B, 1-6 (1944).

8. H. M. Van Dort and H. J. Geursen, Rec. Trav. Chim. Pays-Bas, 86, 520 (1967).

9. P. Jacob, III, P. S. Callery, A. T. Shulgin, and N. Castagnoli, Jr., J. Org. Chem., 41, 3627 (1976).

10. W. Kump and H. Bickel, Helv. Chim. Acta, 56, 2323 (1973). These workers report the following spectroscopic data for 11: ir: 3000, 1680, 1640 and 1635 cm^{-1}; nmr: 12.6 (s, 1H), 11.8 (s, 1H) 6.14 (H-3), 3.42 (OMe), 2.13 (H-14), and 1.73 (H-13); UV (0.01N alcohol HCl): λmax (log ε) 209 (4.41), 287 (4.35), 310 (4.29), and 406 (3.73).

*Notes added in proof.

(Received in USA 13 September 1979)