Tetrahedron Letters, Vol.22, No.26, pp 2451 - 2454, 1981
Printed in Great Britain

0040-4039/81/262451-04$02.00/0

A MODEL STUDY FOR THE BIOMIMETIC-TYPE SYNTHESIS OF RIFAMYCIN S

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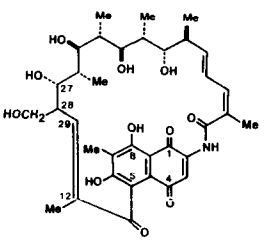
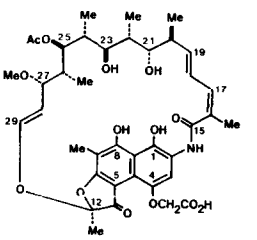
Abstract Acid treatment of the hydroperoxide 5 yielded the enol ether 9. Hydrogenation of 9 gave the dihydro derivative, the structure of which was established by comparison with the substance synthesized by a different route.

White, Martinelli, and Lancini have succeeded in the isolation of rifamycin W (1) by using a mutant strain of Norcardia mediterranei, and have shown that washed mycelium from a rifamycin B producing strain of Norcardia mediterranei transformed rifamycin W into rifamycin B (2).[1,2,3,4]

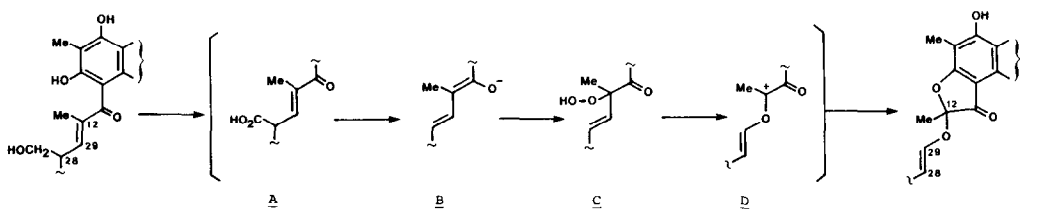


1 : rifamycin W[3,4]



2 : rifamycin B

They have suggested that rifamycin W is a normal intermediate in the biosynthesis of the other rifamycins, and further that a common progenitor is involved in the biosynthesis of the ansamycin antibiotics containing a naphthalene moiety such as rifamycins, streptovaricins, tolypomycins, and halomicins.[5] Related to our investigations on the synthesis of rifamycin S,[6] we were interested in examining the possibility to utilize a compound similar to rifamycin W as an intermediate for a chemical synthesis. A straightforward explanation for the transformation of rifamycin W (1) into rifamycin B (2) would involve the following sequence of reactions:



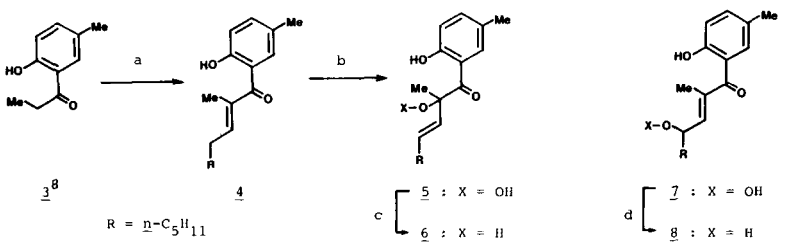
1 : rifamycin W

A B C D

2 : rifamycin B

In this communication, we would like to demonstrate the feasibility of this sequence, at least of its last half, using a model system.

The α,β-unsaturated ketone 4[7] [NMR ($CDCl_3$) δ 0.89 ppm (3H, distorted t), 1.96 (3H, d, J = 1.5 Hz), 2.26 (3H, s), 6.05 (1H, tq, J = 7.0, 1.5)] was prepared from 2-propionyl-p-cresol (3)[8] in 58% overall yield by the method summarized below. The hydroperoxide 5[7] [NMR ($CDCl_3$) δ 0.84 ppm (3H, distorted t), 1.75 (3H, s), 2.28 (3H, s), 5.80 (2H, m), 8.40 (1H, broad s)] was prepared in 61% yield by quenching the anion, generated from 4 with LDA (2.0 eq.), with molecular oxygen. The hydroperoxide 5 was stable enough to isolate by preparative TLC [silica gel/hexane-ether (4-1) and then hexane-ether-chloroform (10-1-50)] and to characterize by spectroscopic means (NMR, IR, UV). Treatment of the hydroperoxide 5 with sodium sulfite in aqueous methanol at room temperature yielded the corresponding alcohol 6[7] [NMR ($CDCl_3$)[9] δ 0.86 ppm (3H, distorted t), 1.72 (3H, s), 2.27 (3H, s), 5.81 (1H, dt, J = 15.7, 1.0 Hz), 5.93 (1H, dt, J = 15.7, 6.5)] in almost quantative yield. Although the olefinic proton signals in the NMR spectrum of 5 were observed as a higher order pattern even with a high field instrument, those of 6 were observed as a well separated spin system, so that the stereochemistry of the olefinic bond of 5 and 6 was conclusively established to be trans (J = 15.7 Hz). It is interesting, particularly related to the biogenetic consideration on the origin of the C-14 hydroxy group of streptovaricins,[5] to point out the fact that the hydroperoxide 5 isomerized, to some extent, to the hydroperoxide 7[7] [NMR ($CDCl_3$) δ 0.90 ppm (3H, distorted t), 2.04 (3H, d, J = 1.5 Hz), 2.27 (3H, s), 4.80 (1H, m), 5.85 (1H, dq, J = 8.0, 1.5), 7.85 (1H, broad s)] when eluted on silica gel plates or even when left standing at room temperature. Reduction of 7 with potassium iodide in methanol gave the corresponding alcohol 8[7].



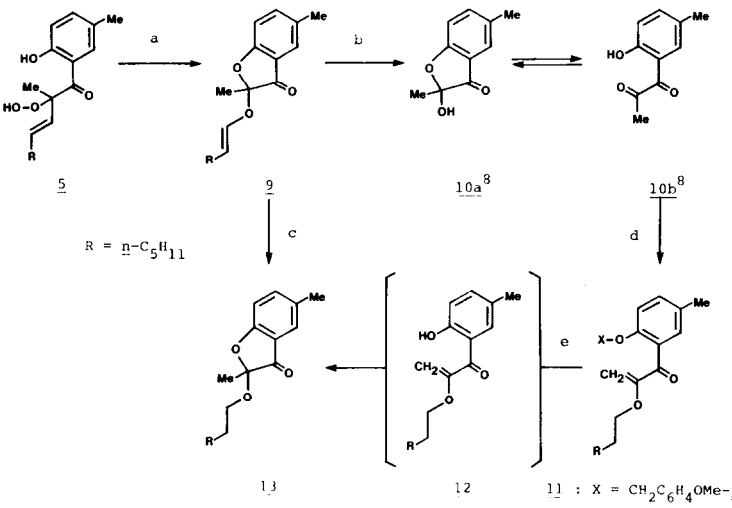
3[8] 4

R = n-C_5H_{11}

Reagents a. 1. p-$MeOC_6H_4CH_2Br/K_2CO_3$/DMF/60°C. 2. LDA/THF/-78°C, followed by addition of $Me(CH_2)_5CHO$ at -78°C. 3. MsCl/$(Et)_3N/CH_2Cl_2$/0°C. 4. DBU/C_6H_6/RT. 5. TFA/CH_2Cl_2/RT.
b. LDA (2.0 eq.)/THF-HMPA (4-1)/-78°C, followed by bubbling oxygen at -78°C.
c. Na_2SO_3/aq. MeOH/RT. d. KI/MeOH/RT.

Brief treatment of the hydroperoxide 5 with acids or acid anhydrides yielded the expected, desired enol ether 9. Among various acidic conditions studied, trifluoroacetic acid (3 eq.) in methylene chloride in the presence of anhydrous magnesium sulfate at 0°C for 45 minutes gave the best result to date; thus, the enol ether 9[7] [Exact MS M^+ observed: 274.1569, M^+ calculated for $C_{17}H_{22}O_3$: 274.1569; NMR ($CDCl_3$) δ 0.82 ppm (3H, distorted t), 1.61 (3H, s), 2.35 (3H, s), 5.25 (1H, dt, J = 12.0, 7.5 Hz), 5.96 (1H, dt, J = 12.0, 1.2); IR (CH_2Cl_2) ν 1725 cm^{-1}] was isolated in 10% yield by preparative TLC [Merck silica gel/hexane-ether (10-1)] in addition to the ketone 10[8] (32% yield), which likely resulted from interception by water of an intermediate like D in

the scheme shown on page one or from hydrolysis of 9, the alcohol 6 (26% yield) and the recovered hydroperoxide (10% yield). The spectroscopic data of 9 were consistent with the assigned structure including the stereochemistry of its olefinic bond.[10] NMR and TLC analysis showed that no cis enol ether was found in this crude reaction mixture.



Reagents a. TFA (3 eq.)/$MgSO_4$/CH_2Cl_2/0°C/45 min. b. aq. TFA/CH_2Cl_2/RT. c. H_2 (1 atm.)/PtO_2/EtOH/RT. d. 1. p-$MeOC_6H_4CH_2Br/K_2CO_3$/DMF/60°C. 2. LDA/THF-HMPA (4-1)/-78°C, followed by addition of $Me(CH_2)_5CH_2I$ at -78°C, and then warmed up to 0°C. e. TFA/C_6H_6/RT.

The structure of 9 was further confirmed from the following experiments. First, acid hydrolysis of 9 (aqueous TFA/CH_2Cl_2/RT) gave the ketone 10[8] and heptanal. Second, hydrogenation of 9 (H_2/PtO_2/EtOH/RT) yielded the dihydro compound 13[7] [63% yield; NMR ($CDCl_3$) δ 0.85 ppm (3H, distorted t), 1.55 (3H, s), 2.34 (3H, s); IR (neat) ν 1720 cm^{-1}], which was found to be identical (NMR, IR, MS, TLC) with the substance prepared by a different route, i.e. 10 → 11 → 13. This route may deserve a few comments. Alkylation of the ketone 10, existing as a tautomeric mixture, under basic conditions took place exclusively at the site of the phenolate anion.[11] The resultant aklylated product (X = p-$MeOC_6H_4CH_2$) was deprotonated with LDA in THF-HMPA, and then treated with heptyl iodide, to yield the enol ether 11[7] [NMR ($CDCl_3$) δ 0.87 (3H, distorted t), 2.28 (3H, s), 3.66 (2H, t, J = 6.5 Hz), 3.79 (3H, s). 4.63 (1H, d, J = 2.5), 4.95 (1H, d, J = 2.5), 4.96 (2H, s)]. Brief acid treatment (TFA/C_6H_6/RT) of 11 afforded the compound 13[7] in 76% yield. This cyclization reaction seemed likely to proceed via compound 12, and hence the choice of protecting group, i.e. p-$MeOC_6H_4CH_2$, of the phenol function was important to achieve this transformation cleanly.[12]

A synthesis of rifamycin S along these lines is currently in progress in our laboratory.

Acknowledgment Financial assistance from the National Institutes of Health (NS 12108) and the National Science Foundation (CHE 78-06296) is gratefully acknowledged.

References and Footnotes

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(2) Protorifamycin I (8-deoxyrifamycin W) was recently isolated by Ghisalba and his co-workers: O. Ghisalba, P. Traxler, and J. Nüesch, J. Antibiotics, 31, 1124 (1978); O. Ghisalba, P. Traxler, H. Fuhrer, and W. Richter, J. Antibiotics, 32, 1267 (1979); O. Ghisalba, P. Traxler, H. Fuhrer, and W. Richter, J. Antibiotics, 33, 847 (1980).

(3) The stereochemistry of the C-28 chiral center and of the C-29 olefinic bond of rifamycin W is unknown (see the paper cited under reference 1).

(4) Numbering of the compounds in this paper corresponds to that of rifamycin S.

(5) For reviews on ansamycin antibiotics, see V. Prelog, Pure Appl. Chem., 7, 551 (1963); K. L. Rinehart, Jr., Acct. Chem. Res., 5, 57 (1972); P. Sensi, Pure Appl. Chem., 41, 15 (1975); K. L. Rinehart, Jr. and L. S. Shield, Prog. Chem. Org. Nat. Prod., 33, 231 (1976); W. Wehrli, Top. Current Chem., 72, 22 (1977).

(6) H. Nagaoka, W. Rutsch, G. Schmid, H. Iio, M. R. Johnson and Y. Kishi, J. Am. Chem. Soc., 102, 7962 (1980); H. Iio, H. Nagaoka, and Y. Kishi, J. Am. Chem. Soc., 102, 7965 (1980); H. Nagaoka, G. Schmid, H. Iio, and Y. Kishi, Tetrahedron Lett., 899 (1981); Y. Kishi, Pure Appl. Chem., in press.

(7) Satisfactory spectroscopic data (MS, NMR, IR, UV) were obtained for this substance.

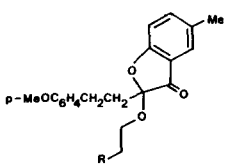
(8) L. Garanti, C. Zecchi, and U. M. Pagnoli, J. Heterocyclic Chem., 14, 445 (1977).

(9) These experiments were performed with a Bruker 300 MHz instrument. We thank Dr. B. Bangerter for measurement of the spectra.

(10) The spin-spin coupling constant of the trans enol ethers is around 12 Hz, while that of the cis enol ethers is around 6 Hz (for some examples, see the paper cited under reference 6).

(11) For the alkylation of this type of compound, see the paper cited under reference 6.

(12) In the presence of $BF_3 \cdot Et_2O$, the enol ether 11 yielded the compound 14. TFA treatment of the enol ether 11 with the benzyl group instead of the p-methoxybenzyl group gave very sluggish results.



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(Received in USA 26 March 1981)