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STUDIES ON THE TOTAL SYNTHESIS OF RIFAMYCIN. HIGHLY STEREOSELECTIVE SYNTHESIS OF INTERMEDIATES FOR CONSTRUCTION OF THE C(15) TO C(29) CHAIN

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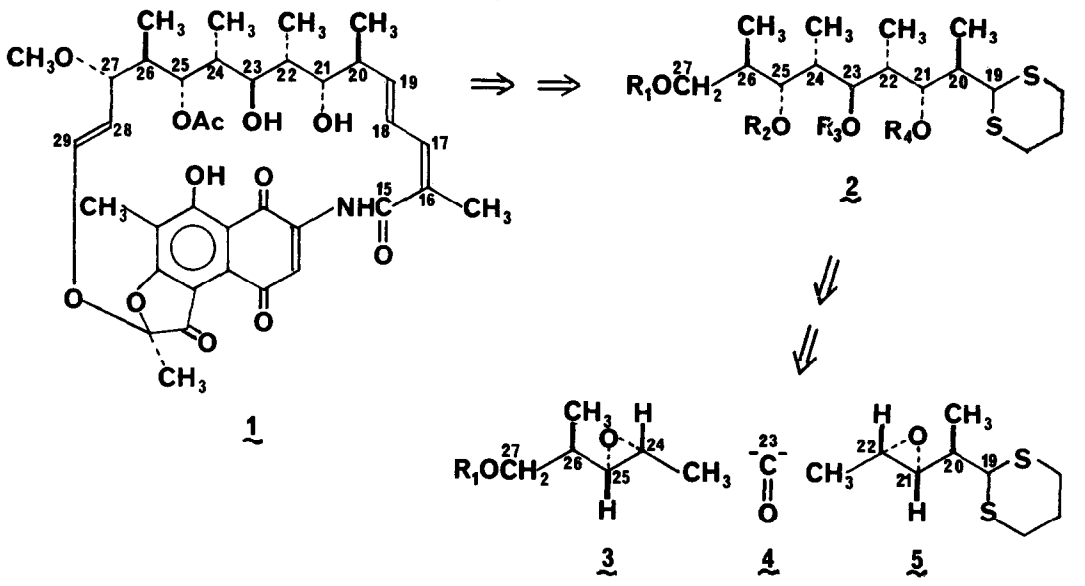
One interesting possibility for the elaboration of the C(15) to C(29) chain of the antibiotic rifamycin S (1)[1] is illustrated by the antithetic relationship indicated in Scheme I. In this plan the

SCHEME I



intermediate 2 which corresponds to the C(19) to C(27) chain is disconnected to a bifunctional nucleophilic carbonyl equivalent (4) and two fragments, 3 and 5 which, except for terminal functional group differentiation, are antipodal. In principle 3 and 5 might be synthesized economically from enantiomeric but otherwise identical 6-carbon precursors. This note presents a solution to the problem of synthesis of 3 and 5 in an efficient and highly stereoselective way which was developed in these Laboratories in the period 1974 - 1975. Although it was our intention to defer publication until synthesis of the complete C(15) to C(29) chain was accomplished, the recent appearance[2] of a related study prompts disclosure of our results at this time.[3]

Reaction of trans-3-pentenoic acid[4] with 2 equiv of lithium diisopropylamide in dry tetrahydrofuran (THF) under argon at 0° C for 1 hr and then excess methyl iodide at 25° C for 1 hr produced trans-2-methyl-3-pentenoic acid (6)[5] in 80-85% yield. Starting with 6, two additional stereocenters could be introduced with high stereoselectivity by means of the halolactonization process. Thus, reaction of the sodium salt of 6 with iodine in methanol-water (85:15) containing sodium bicarbonate at -78° C for 6 hr produced the iodo γ-lactone 7[5] in > 95% yield. The presence of a γ-lactone function was indicated by the appearance of carbonyl absorption in the ir spectrum at 1775 cm^{-1} and the trans-trans arrangement of substituent groups was revealed by the pmr spectrum which showed $J_{H\alpha H\beta}$ = 11 Hz and $J_{H\beta H\gamma}$ = 9 Hz.[6] A trans relationship between H_β and H_γ is also indicated from the known trans addition mode of the halolactonization reaction. The bromo γ-lactone 8 corresponding to iodo lactone 7 could also be obtained in high (85-90%) yield by treatment of the thallium salt of 6 in methylene chloride solution at -78° C with a solution of bromine in methylene chloride. The stereochemistry of 8 (ir max 1775 cm^{-1}, mp 45-46° C) was also clear from the pmr spectrum which showed $J_{H\alpha H\beta}$ = 11 Hz and $J_{H\beta H\gamma}$ = 9 Hz. It seems probable from the conditions involved in the formation of halolactones 7 and 8 that these are kinetically controlled products and that the observed stereoselectivity is not the consequence of equilibration to the thermodynamically favored product. These results contrast with those recently reported[2] for iodo lactonization (under different conditions) of a few γ, δ-unsaturated acids.

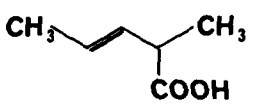
Reduction of the bromo lactone 8 with 1.25 equiv of diisobutylaluminum hydride in petroleum ether at -78° C for 4.5 hr afforded the lactol 9 in 94% yield as a 1:1 mixture of epimers at the anomeric center. The lactol 9 (colorless oil) was not stable to distillation under vacuum, but was sufficiently pure (> 95% by pmr) to be used directly for subsequent reactions. The corresponding iodo lactol was much less stable and for this reason was not studied further. The bromo lactol 9 was converted to the (±)-epoxide-dithiane 5 (80% overall) by the sequence: (1) treatment with 1,3-propanedithiol (1.1 equiv) and boron trifluoride etherate (1 equiv) in benzene for 16 hr, (2) extractive isolation of the resulting dithiane-bromohydrin and (3) reaction with potassium t-butoxide in ether at 25° C for 2-3 hr. Reaction of the bromo lactol 9 with lithium borohydride in ether at 0° C for 3 hr afforded the diol (±)-10 (mp 86° C) which upon treatment with potassium t-butoxide in ether at 25° C for 15 min gave the hydroxy epoxide (±)-3 (R = H) in 94% overall yield.

Thus the two basic components required for the synthesis of 2 are available by a relatively simple and effective route. A number of other protected forms of the epoxy aldehyde unit 5 have been prepared both directly from the lactol 9 and by trans-acetalization of 5 using the method which we have previously described;[3] these include various cyclic and acyclic hemithioketals. In addition the hydroxyl group in 3 (R = H) can readily be protected, e.g., as benzyl or MEM ether. Also, a number of further elaboration products of the lactol 9 have been prepared including 11 and 12, and segments corresponding to 3 and 5 have been joined successfully using deprotonated acetonitrile as the nucleophilic C=O equivalent (4).[7] These results will be discussed later in connection with the completed synthesis of the fragment 2.

Finally, the problem of preparation of optically active intermediates also has been solved. The

racemic acid 6 readily formed a crystalline salt (from ether) with either (+)- or (-)-α-methylbenzylamine. Recrystallization of the salt from the (+)-amine afforded resolved (-)-6 and, similarly, (+)-6 was obtained using the (-)-amine. The absolute configuration of the dextro form of 6 $[\alpha]_D^{23}$ + 63.6° (ether) was determined as being (S) by hydrogenation to the known (S)(+)-2-methylvaleric acid. The absolute configuration of (S)(+)-2-methylvaleric acid follows from its formation by hydrogenation of (S)(+)-2-methyl-4-pentenoic acid which in turn has been correlated (through oxidative C=C cleavage)[8] with (S)(-)-methylsuccinic acid.[9,10] Thus it follows that from (R)(-)-6, the structures having the absolute configuration given by 7-12 and also 5 (the C(24)-C(27) fragment) are available. Further, access to the intermediate 3 (the C(19)-C(22) fragment) is assured starting from (S)(+) -6.

The very effective application of the halolactonization reaction to acyclic systems which is reported herein provides stimulus for the exploration of related examples. We plan to report further progress in this area and also in connection with the synthesis of intermediates leading to rifamycins in due course.[11]



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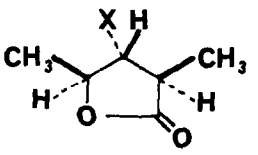
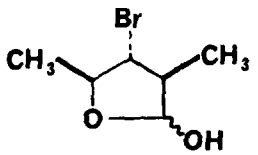


7, X=I
8, X=Br



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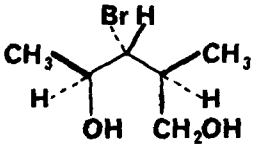

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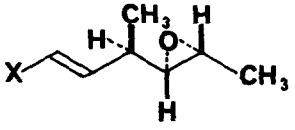
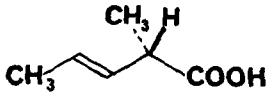


11, X=COOCH3
12, X=CH2OR



(S)(+)-6

References and Notes

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2. P. A. Bartlett and J. Myerson, J. Am. Chem. Soc., 100, 3950 (1978).
3. Mention already has been made by us of acetal exchange reactions of 5 which had been synthesized as described in this paper [see, E. J. Corey and T. Hase, Tetrahedron Lett., 3267 (1975)].
4. Readily prepared by acidic hydrolysis of commercially available trans-3-pentenonitrile; L. Falaise and R. Frognier, Bull. Soc. Chim. Belg., 427 (1933).
5. Satisfactory infrared (ir), proton magnetic resonance (pmr) and mass spectral data were obtained using purified, chromatographically homogeneous samples of the new compounds described herein.
6. See, D. Savostianoff and M. Pfau, Bull. Soc. Chim. France, 4162 (1967) for coupling constants between cis and trans vicinal protons in γ-lactones.
7. Unpublished results by Dr. E. Mihelich in these Laboratories (1976-77).
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10. A. Fredga, Tetrahedron, 8, 126 (1960).
11. We thank the National Institutes of Health for a grant in support of this research, the Fulbright-Hays Program for a Senior Fellowship and travel grant to T. H., and Helsinki University of Technology for a research leave (1974-75).