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STUDIES ON THE TOTAL SYNTHESIS OF RIFAMYCIN. A METHOD FOR THE CLOSURE OF THE MACROCYCLIC UNIT

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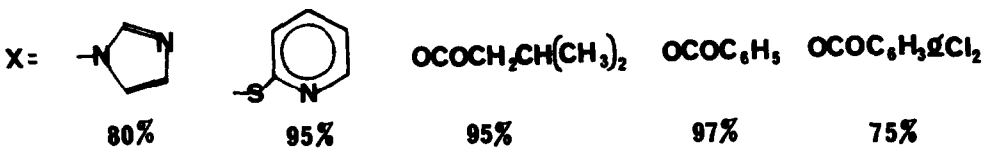
Summary: The formation of the macro ring of rifamycin S (1) has been accomplished by generating the lactam linkage through cyclization of a suitably protected and activated amino acid (4).

Previous papers from these laboratories on the synthesis of rifamycin S (1)[1] have dealt with an approach for the stereocontrolled synthesis of the C(19) to C(27) segment of the ansa bridge[2] and a method for stereospecific chain extension to form the 2Z,4E-dienoyl unit corresponding to C(15) to C(19).[3] Another of the problems to be surmounted by any synthetic attempt, the formation of the macrocyclic unit of 1, has recently been studied and solved. These results which represent another major simplification of the synthetic task are described herein.[4]

Reaction of rifamycin S (1) with excess 2-methoxypropene and 1 equiv of anhydrous copper sulfate in methylene chloride (10 ml/g of 1) at 0° for 4 hr produced rifamycin S-O_{21},O_{23} acetonide 2, mp 180° (dec) in 87% yield.[5,6] This protected derivative was then converted to the amino ester 3 in 80% yield by reaction with 4% sodium hydroxide in methanol at 0° for 8 hr (some deacetylation occurs under these conditions).[7] Attempted saponification of the ester 3 with anaerobic aqueous base under a variety of conditions led only to intractable mixtures.[8] On the assumption that this complication arose because of the base-sensitivity of the amino quinone system a circuitous procedure involving a redox cycle was applied with gratifying success. Treatment of the ester 3 in dimethyoxyethane (DME) with excess 25% aqueous sodium ascorbate (vol ratio 3:1) under argon at at 23° effected reduction of the quinone to the corresponding hydroquinone,[9] to which was added sufficient 4M aqueous lithium hydroxide (air-free) to afford a 1 M solution in base. After 32 hr at 23° (under argon) the mixture was acidified with citric acid, saturated with salt and extracted with ethyl acetate. The organic phase was shaken with aqueous potassium ferricyanide to convert hydroquinone to quinone and the product was isolated and purified by filtration through a column of silica gel (elution with 1:1 methylene chloride-ethyl acetate), to afford in 60% yield the desired 4 admixed with ca. 25% of the corresponding deacetylated acid. Acetylation of the mixture using excess acetic anhydride-pyridine at 23° for 48 hr followed by exposure to a mixture of 10% aqueous sodium hydroxide-tetrahydrofuran (1:2) at 23° for 15 min to cleave phenolic acetate (concurrently

generated) led to the pure amino acid 4. It is noteworthy, but hardly surprising, that the amino function attached to the quinoid ring is quite resistant to acetylation. This observation provided a clear indication that the direct cyclization of the quinoid amino carboxylic 4 would prove difficult.

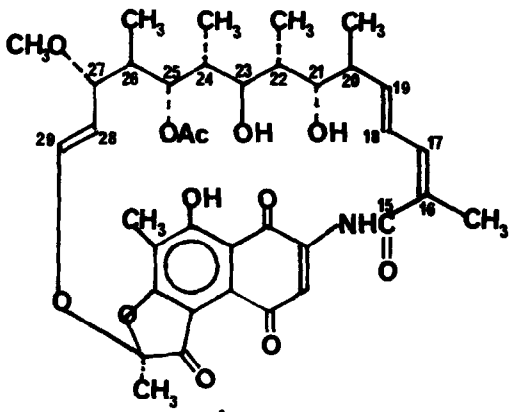
Numerous attempts to effect cyclization of 4 to the ansa-bridged structure 2 under a variety of experimental conditions were uniformly unsuccessful. The following activated carboxylic derivatives, RCOX, were prepared, isolated and characterized spectroscopically (yields indicated).



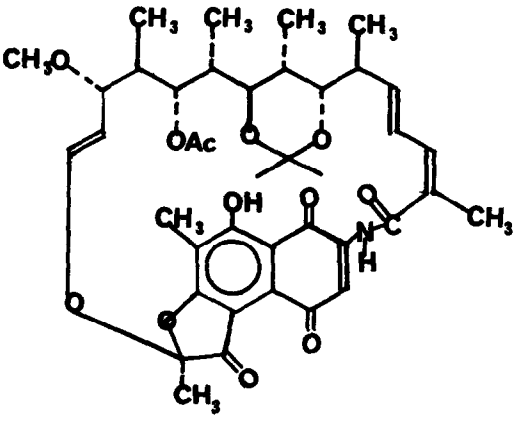
80% 95% 95% 97% 75%

None of these derivatives underwent appreciable cyclization under conditions which seemed most favorable based on previous experience. Again the crux of the problem could be associated with the quinone system which so deactivates the amino group as to prevent its attachment to mildly activated carbocyclic derivatives. Under forcing conditions extensive decomposition occurred. A successful cyclization could be achieved after conversion of the quinone system to the amino hydroquinone form.

Reaction of 4 in ethereal solution at 23° with 1 equiv of triethylamine and 10 equiv of isobutyl chloroformate for 0.5 hr produced the mixed carbonic anhydride of 4 in 95% yield after isolation. This derivative was dissolved in tetrahydrofuran and stirred under hydrogen at 1 atm with palladium-on-calcium carbonate catalyst at -40° for 30 min. After filtration the cold (-78°) solution of hydroquinone was added dropwise over 2 hr via cannula siphon to dry tetrahydrofuran maintained at 50° under argon (with stirring). After an additional 12 hr at 50°, oxidation with aqueous potassium ferricyanide, isolation and purification, the cyclized product 2, the acetonide of rifamycin S, was obtained in 80% yield. Cleavage of the acetonide group in 2 using a mixture of tetrahydrofuran and 3.5% aqueous perchloric acid (5:3) at 23° for 4 hr afforded rifamycin S (95%



1



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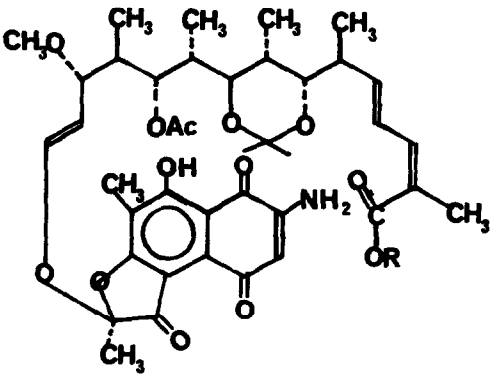

3 R=CH_3
4 R=H

yield) identical in all respects with an authentic sample (including pmr, ^{13}C nmr, ir, chromatographic R_f in 5 different solvents).

The efficient cyclization of the amino acid 4 and further conversion to rifamycin S removes a major obstacle to synthesis. It also provides an encouraging clue that the geometry of the ansa bridge facilitates formation of the macro ring system and that other cyclization processes might function very well, for example an intramolecular closure which generates the phenolic ring concurrently with macrocyclization.[10]

References and Notes

1. W. Oppolzer and V. Prelog, Helv. Chem. Acta, 56, 2279, 2287 (1973); M. Bufani, W. Fedeli, G. Giocomello, and A. Vaciago, Experientia, 20, 339 (1964).

2. E. J. Corey and T. Hase, Tetrahedron Letters, 335 (1979).

3. E. J. Corey and G. Schmidt, Tetrahedron Letters, 2317 (1979).

4. A similar approach to the generation of the macrocyclic unit in the macrolide series produced a key simplification which subsequently led to successful syntheses of erythronolides A and B; see, (a) E. J. Corey, P. B. Hopkins, S. Kim, S. Yoo, K. P. Nambiar, and J. R. Falck, J. Am. Chem. Soc., 101, 7131 (1979); (b) E. J. Corey, E. J. Trybulski, L. S. Melvin, K. C. Nicolaou, J. A. Secrist, R. Lett, P. W. Sheldrake, J. R. Falck, D. J. Brunelle, M. Haslanger, S. Kim and S. Yoo, J. Am. Chem. Soc., 100, 4618 (1978); and (c) E. J. Corey, S. Kim, S. Yoo, K. C. Nicolaou, L. S. Melvin, D. J. Brunelle, J. R. Falck, E. J. Trybulski, R. Lett, and P. W. Sheldrake, J. Am. Chem. Soc., 100, 4620 (1978).

5. (a) This procedure was developed in these laboratories by Mr. Stephen S. Kamin; (b) see also W. Kemp and H. Bickel, Helv. Chem. Acta, 56, 2323 (1973).

6. All isolated substances described herein were characterized by infrared, proton magnetic resonance and mass spectrometric data which were in full accord with the assigned structures.

7. The acetoxy group at C(25) in the acetonides 2 and 3 is remarkably resistant to base.

8. Other reagents for methyl ester cleavage, e.g. trimethylsilyl iodide, lithium n-propylmercaptide in hexamethylphosphoric triamide, lithium iodide-pyridine, were also ineffective.

9. The hydroquinone is rapidly oxidized by air which therefore had to be excluded rigorously.

10. This research was assisted financially by the National Institutes of Health.

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