Tetrahedron Letters No. 25, pp 2317 - 2320. 0040-4039/79/0615-2317$02.00/0

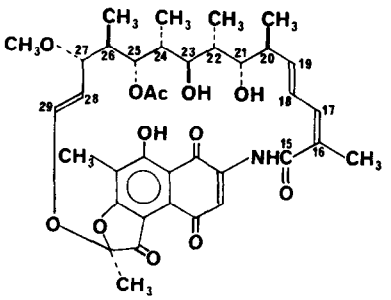
STUDIES ON THE TOTAL SYNTHESIS OF RIFAMYCIN. A METHOD FOR THE STEREOSPECIFIC SYNTHESIS OF THE CARBONYL-CONJUGATED 1,3-DIENE UNIT [C(15) to C(20)]

E. J. Corey and Greg Schmidt

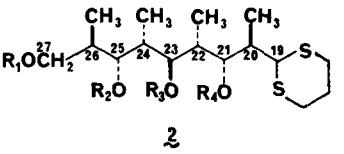
Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138, USA

Summary: A new stereospecific process has been devised for the conversion of an aldehyde to a 5-substituted-2-methyl-2 Z, 4 E-pentadienoic acid. This methodology is relevant to the construction of the ansa bridge of the rifamycins.

The synthesis of rifamycin S (1)[1] presents a major challenge to present chemical practice. In a previous paper an approach has been outlined for the construction of the key intermediate 2 which contains carbons 19 to 27 of the ansa bridge unit of the rifamycins. Inherent in the plan to utilize 2 as a precursor

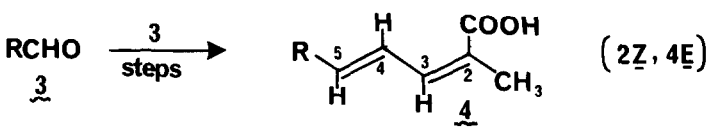


1

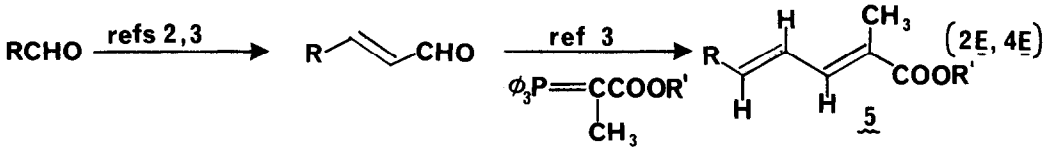


2

of rifamycins is the requirement of a further elaboration at some stage to add carbons 15 to 18 in the correct stereochemical arrangement. This report presents a new and stereospecific method for this elaboration which can be formulated in a general sense as the overall chain extension 3 → 4. This construction has not



previously been accomplished in a stereospecific way despite the availability[2,3] of several Wittig-type methods which produce selectively the isomeric (and more stable) 2 E, 4 E-dienoic acids (5), for example:

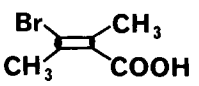


The process for the transformation 3 → 4 as herein disclosed depends on the key reagent ethyl E-2-methyl-3-methylthio-2-butenoate (7) which contains all the carbon atoms needed for chain extension. The reagent 7 is readily available from the known bromo acid 6[4] in 98% overall yield by the sequence (1) esterification with 3 equiv of ethyl iodide and 1.5 equiv of potassium carbonate in dimethylformamide (DMF) (2 ml/g of 6) at 25° C for 24 hr to afford quantitatively ethyl β-bromo-angelate[5] and (2) reaction in ethanol with sodium methyl mercaptide (from 1.5 equiv of sodium ethoxide in ethanol and a slight excess of methyl mercaptan) under nitrogen for 30 hr.[6,7]

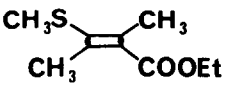
γ-Deprotonation of 7 could be effected cleanly by slow addition under argon to a stirred solution of 1.02 equiv of lithium diisopropylamide in dry tetrahydrofuran (THF) maintained at -95° C (hexane-liquid nitrogen slush) to give a pale yellow solution of the lithio derivative. Addition of 1 equiv of cyclohexane carboxaldehyde in a little dry THF to a solution of lithiated 7 at -95° C followed by reaction at -95° C for 15 min and at -95 to -20° C (gradual warming) for 90 min afforded after quenching with ammonium chloride, extractive work-up and chromatographic purification on a silica gel column with 3:1 hexane-ether as eluant the lactone 8[7] (72%)[8] as a crystalline solid, mp 55-56° C, infrared max 1697 cm.$^{-1}$ ($CHCl_3$).[9,10] Desulfurization of 8 was effected quantitatively by treatment with deactivated W-2 Raney nickel[11] in acetone at 25° C with stirring until thin layer chromatographic (tlc) analysis indicated the complete consumption of starting material (R_f 0.22 for 8 vs. R_f 0.32 for product using hexane-ether 2:1) (time required ca. 15 min) to yield the lactone 9, mp 46-48° (solidifies after isolation), infrared max 1709 cm.$^{-1}$ ($CHCl_3$), pmr peaks due to vinyl at 6.54 ppm and methyl at 1.87 ppm (mult.) (in $CDCl_3$), ultraviolet max ~215 nm. Reaction of 9 in dry THF at 0° C with a solution of 2.1 equiv of potassium t-butoxide in THF with stirring under argon for 10 min at 0° C and 0° to 25° C for 15 min followed by quenching with ammonium chloride and extractive isolation resulted in E2-type elimination to give the diene acid 10 (79%) as a crystalline solid, mp 81-83° C; ultraviolet max at 263 nm (24, 800) (in CH_3CN); infrared max at 1672, 1629 and 1596 cm.$^{-1}$ (in $CHCl_3$). Pmr measurements of 10 (in $CDCl_3$) provided the following data after complete spin decoupling: δH_b 7.24, δH_a 6.56, δH_c 5.97, δCH_3 1.98 ppm; J_{ab} 11.3 Hz, J_{bc} 15.2 Hz, J_{cd} 7.0 Hz, $J_{a\text{-}CH_3}$ 1.4 Hz, $J_{b\text{-}CH_3}$ 1.1 Hz. The stereochemistry of 10 (expected from the mode of formation) is confirmed by these data which compare closely with the pmr data for seco diene esters derived from rifamycin S.[12]

The same reaction sequence was also performed successfully with a protected β-hydroxy aldehyde chosen to serve as a model of the substrate derived by dithiane cleavage of 2. Ethyl 3-hydroxy-2-methyl-butanoate[13] (mixture of diastereomers) was converted to the t-butyldimethylsilyl ether 11 (92% yield) by reaction with t-butyldimethylsilyl chloride-imidazole[14] in DMF at 0° C for 13 hr. Reduction of the ester 11

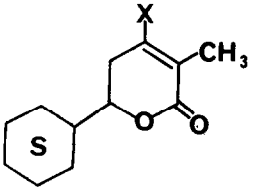
in toluene at -78° C with diisobutylaluminum hydride (1.2 equiv) afforded cleanly the model aldehyde 12[15] which could be utilized without purification. (Chromatography on silica gel results in considerable oxidative loss of material since pure aldehyde could be obtained in only 72% yield starting from 11 of > 95% purity.) It was also noted that 12 is very prone to oxidation by air. Addition of freshly prepared protected aldehyde 12[15] dissolved in a little toluene to the lithio derivative of 7 in THF at -95° C under argon (vide supra), subsequent reaction at -95° C for 15 min and -95 to -20° C over a 90 min period and quenching with saturated aqueous ammonium chloride produced after extractive work-up and chromatography on silica gel (3:1 hexane-ether for elution) the α-lactone 13[15] (60% yield) as a colorless oil, infrared max 1701, 1599 cm.$^{-1}$ ($CHCl_3$), and ultraviolet max 280 nm in CH_3CN. Desulfurization of 13 as described above for 8 afforded in > 99% yield the required lactone 14[15] as a colorless oil (R_f 0.26 in CH_2Cl_2 as compared to 0.30 for 13), infrared max 1713 cm.$^{-1}$ ($CHCl_3$), ultraviolet max 215 nm in CH_3CN, pmr olefinic proton multiplet at 6.57 ppm and methyl on C=C at 1.90 ppm ($CDCl_3$). The lactone 14 upon reaction with potassium t-butoxide in THF as described above for the preparation of 10, afforded the diene acid 15[15] as a white solid (84% yield), infrared max 1678, 1631, 1598 cm.$^{-1}$ (CH_2Cl_2), ultraviolet max 263 nm (CH_3CN), homogeneous by tlc analysis in 5 solvent systems. The pmr spectrum of 15 in the vinyl region was superimposable with that for 10, confirming that the required olefinic geometry was achieved stereospecifically.



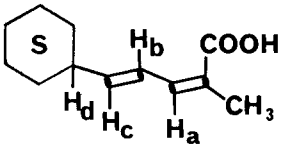
6



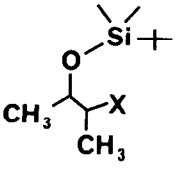
7



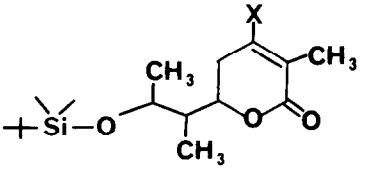
8, X = SCH_3
9, X = H



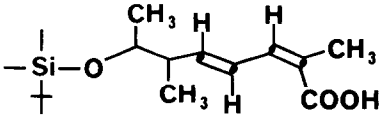
10



11, X = COOEt
12, X = CHO



13, X = SCH_3
14, X = H



15

The transformations delineated herein provide methodology for the synthesis of the ansa-bridge unit of the rifamycins which should be of value in a wide variety of synthetic approaches. In a paper which is to be presented in the near future there is outlined a more standard five-step process which utilizes standard Wittig condensations for the generation of 2,4-pentadienoic units.[16] As is to be expected this sequence is completely non-stereoselective.[17]

References and Notes

1. W. Oppolzer and V. Prelog, Helv. Chim. Acta, 56, 2279, 2287 (1973); M. Brufani, W. Fedeli, G. Giocomello, and A. Vaciago, Experentia, 20, 339 (1964).
2. E. J. Corey and M. G. Bock, Tetrahedron Lett., 2643 (1975).
3. W. S. Wadsworth, Jr., Org. Reactions, 25, 73 (1977).
4. For preparation see, R. E. Buckles and G. V. Mock, J. Org. Chem., 15, 680 (1950).
5. (a) J. S. Pizey and W. E. Truce, J. Chem. Soc., 865 (1964) and (b) C. Chalchat, P. Duteurtre, F. Théron, and R. Vessiére, Rec. Trav. Chim. Pays Bas, C, 273, 832 (1971).
6. J. C. Chalchat and F. Théron, Bull. Soc. Chim. France, 95 (1974).
7. Satisfactory infrared, proton magnetic resonance, and mass spectral data were obtained for each new substance reported herein using purified, chromatographically homogeneous samples.
8. Yield refers to consumed starting aldehyde since some cyclohexane carboxaldehyde was recovered in chromatographic purification.
9. An analogous γ-hydroxyalkylation of the lithio derivative of ethyl β-methoxycrotonate with aldehydes had earlier been noted by E. E. Smissman and A. N. Voldeng [J. Org. Chem., 29, 3161 (1964)] to afford 3-alkoxy-2,4-dienoic acids. However, the intermediate δ-lactones could not be isolated in these studies.
10. The procedure used for this process was patterned after one developed in these laboratories by Mr. John M. Maher for the conversion of ethyl β-methoxycrotonate to the lithio derivative and further reaction with aldehydes to give 5-substituted 3-methoxy-Δ^2-dehydro-δ-valerolactones. Another approach to 3-methoxy-Δ^2-dehydrovalerolactones has been developed by R. M. Carlson, A. R. Oyler and J. R. Peterson, J. Org. Chem., 40, 1610 (1975).
11. Freshly prepared W-2 Raney nickel was deactivated by stirring with acetone for 1.5 hr at 25° C. Aged samples of Raney nickel require less deactivation.
12. See, W. Oppolzer and V. Prelog, Helv. Chim. Acta, 56, 2287 (1973).
13. Prepared in 90% yield by the reduction of ethyl acetopropionate with sodium borohydride in 95% ethanol at -25° C for 30 min.
14. E. J. Corey and A. Venkateswarlu, J. Am. Chem. Soc., 94, 6190 (1972).
15. Diastereomeric mixture.
16. See, M. Kinoshita, N. Nakata, T. Sakai, and K. Tatsuta, Organic Abstracts, Joint Meeting of the American Chemical Society and the Chemical Society of Japan, April 1979, Abstract No. 481.

17. This research was assisted financially by a grant from the National Institutes of Health.

(Received in USA 19 March 1979)