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PARTIAL SYNTHESIS OF FUSIDIC ACID[1]

Masato Tanabe,* Dennis M. Yasuda and Richard H. Peters
Stanford Research Institute
333 Ravenswood Avenue
Menlo Park, California 94025

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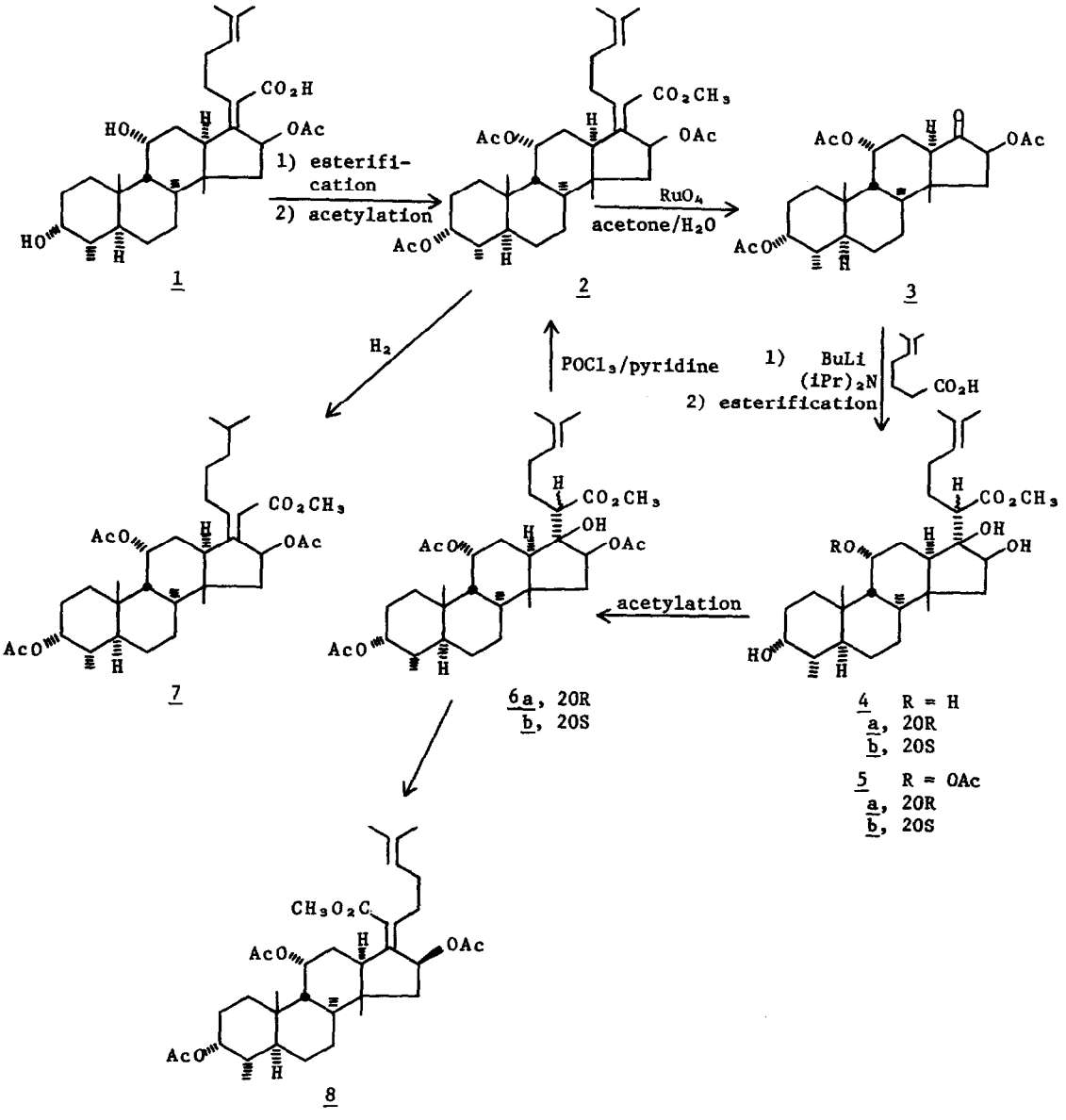
The structural elucidation of a closely related group of steroidal antibiotics, fusidic acid[2] (1), cephalosporin P.,[3] and helvolic acid[4] has established that these antibiotics possess unique structures and stereochemistry. Recent attention has focused on the synthesis of the novel tetracyclic trans, syn, trans ring system of fusidic acid[5,6] (1). The two reported syntheses have as an intermediate target a tetracyclic steroid skeleton bearing a C-17 ketone function for ultimate elaboration to fusidic acid. We wish to report a successful synthetic method for introduction of the characteristic 17(20)Z isooctenoic acid side chain of these antibiotics on to a tetracyclic intermediate, such as the C-17 ketone (3).

The tetracyclic C-17 ketone (3),[7] which can also serve as a convenient relay intermediate, was obtained from the methyl ester of diacetoxyfusidic acid (2) by oxidative cleavage of the $\Delta^{17(20)}$ bond with ruthenium tetraoxide.[8] The product was isolated by silica gel column chromatography eluting with 10% ether-benzene. The CD spectrum [CD-curve: λ^{dioxane} 298 nm ($\Delta\varepsilon$ = -4.15)], of ketone 3 indicated that the C-13α stereochemistry of fusidic acid was retained. This result is in agreement with previously reported work.[9]

We have previously reported that the addition of lithium α-lithiopropionate to C-17 ketones in the androstane series offers a convenient route to 17β-hydroxybisnorcholanic acid derivatives.[10] Extension of this reaction to the addition of the lithium dianion of 6-methyl-5-heptenoic acid to the C-17 ketone (3) was investigated for application to fusidic acid synthesis.

The desired 6-methyl-5-heptenoic acid[11] was conveniently prepared in 50% yield by the reaction of 1-bromo-4-methyl-3-pentene[12] with the dilithium salt of acetic acid in tetrahydrofuran.[13] Lithium 2-lithio-6-methyl-5-heptenoate was then generated in the usual manner with lithium diisopropylamide in THF and condensed with the C-17 ketone (3) to give after esterification with methyl iodide and sodium bicarbonate in dimethylacetamide a stereoisomeric mixture


1) esterifi-
cation
2) acetylation
RuO4
acetone/H2O
H2
POCl3/pyridine
1) BuLi
(iPr)2N
2) esterification
acetylation
1
2
3
7
6a, 20R
b, 20S
4 R = H
a, 20R
b, 20S
5 R = OAc
a, 20R
b, 20S
8

Scheme 1

of the tetrol 4 and its monoacetate 5 as the major products. The tetrol 4 was isolated as a mixture (1:1) of 4a and 4b in 22% yield by preparative tlc (silica gel) using a 50% ether-benzene solvent system. The monoacetate 5 proved to be the 11-acetate based on nmr chemical shift data as previously reported.[7] The monoacetate 5 (Calcd. for $C_{32}H_{52}O_7$: C, 70.04; H, 9.55. Found: C, 70.05; H, 9.54) was a mixture of two stereoisomers 5a and 5b (20% yield of each) which were separable by preparative tlc (50% ether-benzene). These isomers were considered to be C-20 stereoisomers from their nmr spectra. The nmr spectra of each isomer isolated by preparative tlc were identical except for the chemical shifts of their C-16 protons (4.50 and 4.18 ppm) and their C-8α angular methyls (1.26 and 1.32 ppm) and were consistent with their proposed structures with C-17α oriented side chains. From inspection of models of both isomers in a hydrogen-bonded rotamer form[9] between the C-20 carboxyl and C-17β hydroxyl, it appears that the different chemical shifts of the C-8 α-angular methyls in the two isomers result from their interaction with the C-17 α-oriented isooctenoic acid side chain. Presumably if the side chain were β-oriented, the resonance of the C-14 β angular methyl would not be expected to remain constant as found. It appears therefore that the two components of 5 are enantiomeric around C-20 and not C-17.

Isomer 5a, nmr ($CDCl_3$): 1.13 (14β-CH_3), 1.26 (8α-CH_3), 2.03 (11-OAc), 4.50 (d, J = 8 Hz, C_{16}-H), 5.27 (C_{11}-H), was acetylated with acetic anhydride in pyridine to afford the 3α,11α, 16β-triacetoxy derivative 6a. The triacetate 6a was dehydrated with phosphorus oxychloride in pyridine to give, after preparative thin-layer chromatography, an oil (2) (30% yield), which was identical to authentic methyl diacetoxyfusidate obtained directly from esterification and acetylation of fusidic acid. Our attempts to crystallize the oil were not successful; other previously reported attempts were also unsuccessful.[7] The methyl ether triacetates (2) obtained from compounds 6a and 1 were separately hydrogenated to yield crystalline 24,25 dihydro derivatives 7 which were identical in all respects.

If the dehydration of 6a with phosphorus oxychloride to methyl diacetoxyfusidate 2 involves a transition state in which the C-20 proton assumes a trans position relative to the 17β-hydroxyl group, then 6a would have the 20R configuration.

Isomer 5b, nmr ($CDCl_3$): 1.13 (14β-CH_3), 1.32 (8α-CH_3), 2.03 (11-OAc), 4.18 (d, J = 8 Hz, C_{16}-H), 5.26 (C_{11}-H), was similarly acetylated to afford 6b. In contrast, dehydration of isomer 6b yielded methyl diacetoxylumifusidate (8), (17*E*), nmr ($CDCl_3$): 2.03 (16-OAc), 3.71 (methyl ester), and 5.69 (d, J = 8 Hz, C_{16}-H). From this data 6b was assigned the 20S configuration and the structure is in agreement with the spectral and chemical data. An authentic sample of 8 was synthesized by esterification and acetylation of lumifusidic acid,[14] and was found to be identical with the product from the dehydration of the 20S isomer of 6b.

This successful transformation of 3 to the required $\Delta^{17(20)}$ unsaturation and Z-stereochemical configuration of the isooctenoic acid side chain thus offers the means to complete any total synthetic effort towards these antibiotics from a tetracyclic target compound[15] having a C-17 ketone.

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REFERENCES AND NOTES

1. This work was supported by the Public Health Service under Grant AI 07397 from the National Institute of Allergy and Infectious Diseases.
2. W. O. Godtfredsen and S. Vangedal. *Tetrahedron* 18, 1029 (1962).
3. H. S. Burton, E. P. Abraham, and H.M.E. Cardwell. *Biochem.* 62, 171 (1956).
4. S. Okuda, S. Iwasaki, M. I. Sair, Y. Machida, A. Inoue, K. Tsuda, and Y. Nakayama. *Tetrahedron Letters*, 2295 (1967).
5. W. G. Dauben, G. Ahlgren, T. J. Leitereg, W. C. Schwarzel, and M. Yoshioka. *J. Amer. Chem. Soc.* 94, 8593 (1972).
6. R. E. Ireland and U. Hengartner. *J. Amer. Chem. Soc.* 94, 3652 (1972).
7. P. A. Diassi, I. Bacso, G. W. Krakower, and H. A. Van Dine. *Tetrahedron* 22, 3459 (1966).
8. R. C. Ebersole, W. O. Godtfredsen, S. Vangedal, and E. Caspi. *J. Amer. Chem. Soc.* 95, 8133 (1973).
9. W. O. Godtfredsen, W. von Daehne, S. Vangedal, A. Marquet, D. Arigoni, and A. Melera. *Tetrahedron* 21, 3505 (1965).
10. M. Tanabe and R. H. Peters. *J. Org. Chem.* 36, 2403 (1971).
11. M. F. Ansell and S. S. Brown. *J. Chem. Soc.*, 1788 (1957).
12. M. Julia, S. Julia, and R. Guégan. *Bull. Soc. Chim. Fran.*, 1072 (1960).
13. P. L. Creger. *J. Amer. Chem. Soc.* 89, 2500 (1967).
14. W. O. Godtfredsen, W. von Daehne, L. Tybring, and S. Vangedal. *J. Med. Chem.* 9, 15 (1966).
15. We have converted methyl diacetoxy fusidate to fusidic acid by selective saponification procedures. Thus this synthesis offers a relay route for any formal total synthesis of fusidic acid.