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TRANSFORMATION OF 3-O-MYCAROSYLERYTHRONOLIDE B, AN INTERMEDIATE OF ERYTHROMYCIN BIOGENESIS, INTO 3-O-MYCAROSYL-(8S)-8-FLUOROERYTHRONOLIDE B USING TRIFLUOROMETHYL HYPOFLUORITE

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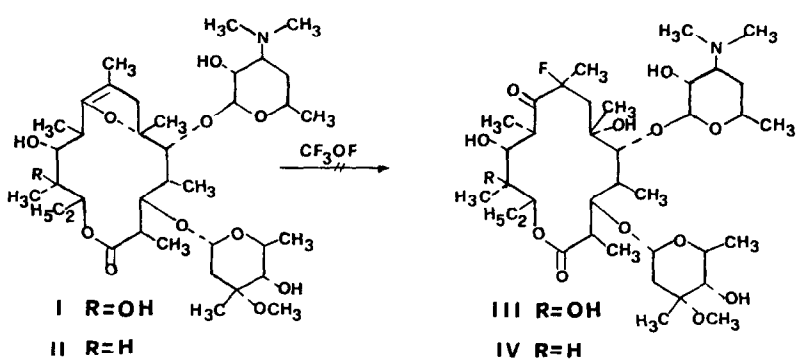
Summary: Treatment of 3-O-mycarosylerythronolide B (V) with glacial acetic acid gave 3-O-mycarosyl-8,9-anhydroerythronolide B 6,9-hemiketal (VI) together with 3-O-mycarosylerythronolide B 6,9; 9,11-spiroketal (VII). Fluorination of VI with trifluoromethyl hypofluorite (CF_3OF) gave a mixture of 3-O-mycarosyl-(8S)-8-fluoroerythronolide B (IX) and 3-O-mycarosyl-(8S)-8-fluoroerythronolide B 6,9;9,11-spiroketal (X) (major product).

We have previously reported[1] that trifluoromethyl hypofluorite (CF_3OF)[2] reacts readily with 8,9-anhydroerythronolide A and B 6,9-hemiketals to give (8S)-8-fluoroerythronolides A and B and (8S)-8-fluoroerythronolide A and B 6,9;9,11-spiroketals, respectively. This reaction was of interest to us per se and also as a model for the reaction in the erythromycin series.

In studying the fluorination of 8,9-anhydroerythromycin A 6,9-hemiketal (I, Scheme 1)[3] with

Scheme 1

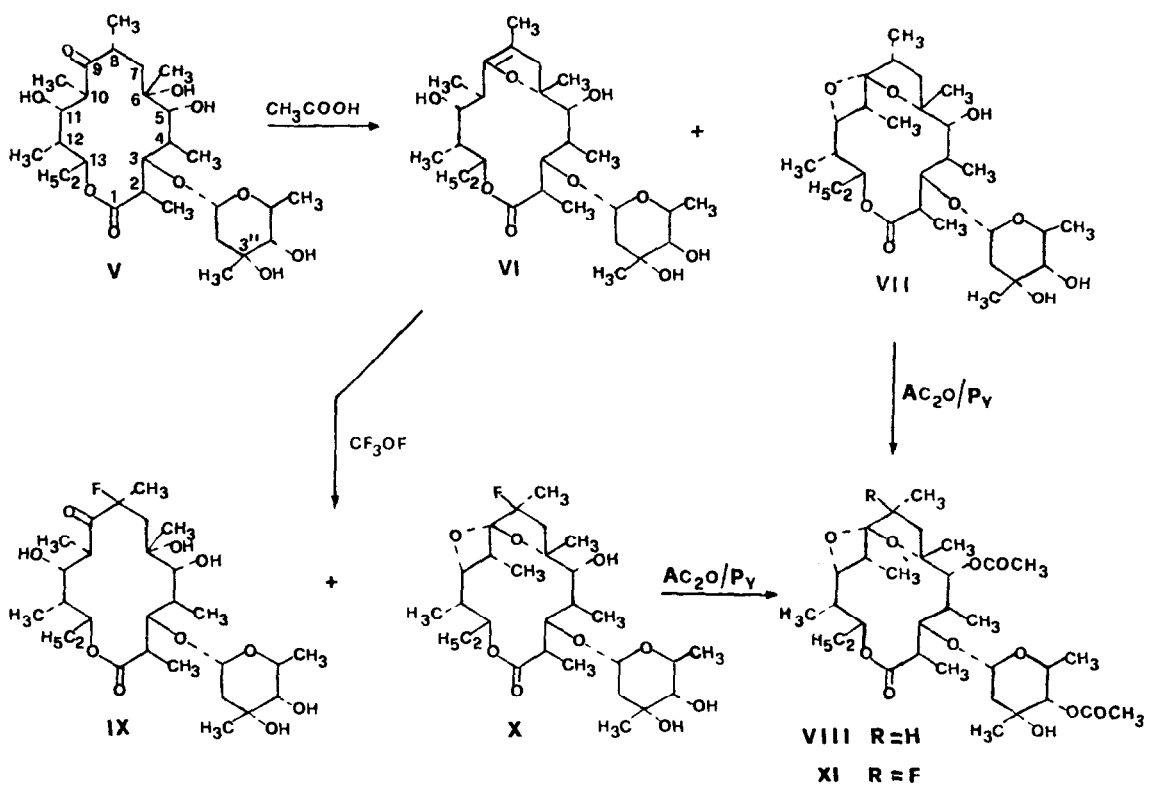


CF_3OF in the usual manner (dichloromethane - Freon 11 1:1, 0.5 hours, -80°C)[1], attempts were

made to isolate (8S)-8-fluoroerythromycin A (III) from the final solution, but a complex mixture of products was isolated and shown by thin layer chromatography (TLC)[4] to contain no III. In fact, all the products present in the reaction mixture showed a TLC migration much slower than that of erythromycin A while one would be expect this latter and (8S)-8-fluoroerythromycin A (III) to have similar Rfs, since fluorine is isosteric with hydrogen [1]. When we carried out an analogous fluorination on the enol ether group of 8,9-anhydroerythromycin B 6,9-hemiketal (II)[3] a similar behaviour was observed. These results suggested that other reaction sites in 8,9-anhydroerythromycin A and B 6,9-hemiketals (I and II) were readily accessible to the CF_3OF reagent, besides the double bond of the enol ether. A likely possibility was the N-demethylation of desosamine mediated by the fluorinating agent with a mechanism analogous to the oxidative removal by iodine or bromine of N-methyl groups from the 3'-dimethylamino moiety of the mycaminose or desosamine residue of macrolide antibiotics[5].

In order to verify this hypothesis, fluorination of 3-O-mycarosyl-8,9-anhydroerythronolide B 6,9-hemiketal (VI) was attempted (Scheme 2).

Scheme 2



Treatment of 3-O-mycarosylerythronolide B (V)[6,7] under conditions which readily convert erythromycin A and erythromycin B to their corresponding enol ethers (glacial acetic acid, 2 hours, room temperature)[3] gave a mixture containing 25% of 3-O-mycarosyl-8,9-anhydroerythronolide B 6,9-hemiketal (VI), m.p. 86-8°C (from hexane), $[\alpha]_D^{20}$ -4.9° (c 1.0, methanol), (Found: C 63.52; H 9.09. Calc. for $C_{28}H_{48}O_9$: C 63.61; H 9.15) and 13% of 3-O-mycarosylerythronolide B 6,9;9,11-spiroketal (VII), m.p. 166-7°C (from hexane), $[\alpha]_D^{20}$ - 5,9° (c 1.0, methanol), (Found: C 63.62; H 8.96. Calc. for $C_{28}H_{48}O_9$:C 63.61; H 9.15). These two compounds and some unreacted starting product V (45%) were isolated by column chromatography on silica gel (ratio 1 : 100), using chloroform-methanol (99 :1) as eluent. The enol ether structure of VI was determined from its ultraviolet spectrum in methanol[3,8], 210 nm (ε 6850). In contrast, product VII did not exhibit characteristic UV maxima. This observation together with the microanalytical results led to the tentative assignment of the spiroketal structure of VII. The study of the 60 MHz ^{1}H-NMR spectra and acid hydrolysis patterns of these compounds provided further evidence for their structures. Comparison of their chemical shifts and coupling constants with those of 8,9-anhydroerythronolide B 6,9-hemiketal[8] and erythronolide B 6,9;9,11-spiroketal[9] revealed striking similarities. As previously reported for 8,9-anhydroerythronolide B 6,9-hemiketal[8] and erythronolide B 6,9;9,11-spiroketal[9], compounds VI and VII were completely converted to erythronolide B after 22 hours in aqueous methanolic hydrochloric acid. The definitive structural assignment of 3-O-mycarosylerythronolide B 6,9; 9,11-spiroketal (VII) was obtained from the ^{1}H-NMR spectrum of its acetyl derivative (VIII). By treatment with acetic anhydride in pyridine[10] the spiroketal VII was converted into the 4",5-di-O-acetyl derivative VIII, m.p. 209-10°C (from hexane), $[\alpha]_D^{20}$ - 51.2° (c 1.0, methanol), (Found: C 62.58; H 8.38. Calc. for $C_{32}H_{52}O_{11}$: C 62.72; H 8.55). Comparison of the ^{1}H-NMR (pyridine-d_5) resonances of the C-11 protons of VII and VIII (δ 4.80 and 4.15 ppm, respectively) showed that on acetylation of the C-11 hydroxyl group the expected downfield shift[11] did not occur. On the contrary, downfield shifts of the C-4" and C-5 protons resonances were caused by acetylation of the secondary hydroxyl groups.

Fluorination of VI with CF_3OF (dichloromethane - Freon 11 1:1, 0.5 hours, -80°C)[1] gave a 1:9 mixture of IX and X, shown by high performance liquid chromatographic monitoring[4] of the reaction mixture. Column chromatography on silica gel (ratio 1 : 100), using chloroform-methanol (99 : 1) as eluent, gave 5% of 3-O-mycarosyl-(8S)-8-fluoroerythronolide B (IX), m.p. 214-5°C (from acetone-hexane), $[\alpha]_D^{20}$ - 73.2° (c 1.0, methanol), UV (methanol) 286-8 nm (ε 34), (Found: C 59.55; H 8.75; F 3.37. Calc. for $C_{28}H_{49}FO_{10}$: C 59.68; H 8.60; F 3.48) and 58% of

3-O-mycarosyl-(8S)-8-fluoroerythronolide B 6,9;9,11-spiroketal (X), m.p. 176-8°C (from diethyl ether-hexane), $[\alpha]_D^{20}$ - 9,8° (c 1.0, methanol), (Found: C 61.46; H 8.51; F 3.48. Calc. for $C_{28}H_{47}FO_9$: C 61.52; H 8.67; F 3.47). In aqueous methanolic hydrochloric acid[9] for 24 hours, IX and X were converted to (8S)-8-fluoroerythronolide B[1] and (8S)-8-fluoroerythronolide B 6,9;9,11-spiroketal[1], respectively. Examination by thin-layer chromatography[12] of the products formed by mild acidic methanolysis of IX and X showed also the presence of the α and β anomers of L-methylmycaroside identical with those obtained from 3-O-mycarosylerythronolide B (V) under the same conditions. The spiroketal X was converted into the 4",5-di-O-acetyl derivative XI[13] by treatment with acetic anhydride in pyridine[10]. The two compounds showed similar ^{1}H-NMR behaviour to VII and its acetyl derivative VIII.

These results indicated that during the fluorination of I or II the displacement of one or both the methyl groups of the desosamine moiety is very likely to occur. Studies in this area are continuing with the aim of producing new fluoro-erythromycins.

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