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PREPARATION OF (8S)-8-FLUOROERYTHRONOLIDE A AND (8S)-8-FLUOROERYTHRONOLIDE B, POTENTIAL SUBSTRATES FOR THE BIOLOGICAL SYNTHESIS OF NEW MACROLIDE ANTIBIOTICS

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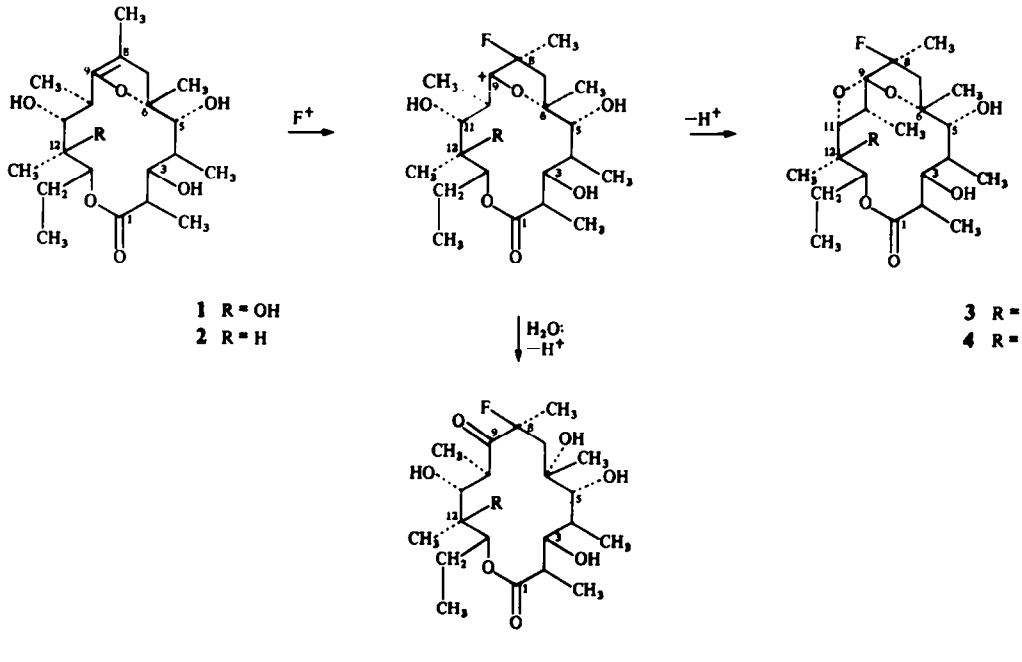
Abstract—Synthetic studies are reported in the erythromycin analogue area. Reaction of trifluoromethyl hypofluorite (CF_3OF) with 8,9-anhydroerythronolide A 6,9-hemiketal (**1**) or 8,9-anhydroerythronolide B 6,9-hemiketal (**2**) afforded, as major product, (8S)-8-fluoroerythronolide A 6,9;9,11-spiroketal (**3**) or (8S)-8-fluoroerythronolide B 6,9;9,11-spiroketal (**4**) and, as minor product, (8S)-8-fluoroerythronolide A (**5**) or (8S)-8-fluoroerythronolide B (**6**). Hydrolysis of **3** in boiling aqueous acetic acid gave **5**, 9,10-anhydro-(8S)-8-fluoroerythronolide A 6,9-hemiketal (**7**), (8S)-8-fluoroerythronolide A 5,9;9,12-spiroketal (**9**) and 5,8-epoxy-8-*epi*-erythronolide A (**10**). Analogous range of products was obtained by acid hydrolysis of **4**.

Recently[1] synthetic modifications of the erythromycin aglycon fragments have been investigated in our laboratory in order to prepare new macrolide antibiotics through a chemical-biological route. The present report concerns with the preparation of (8S)-8-fluoroerythronolide A (**5**) and (8S)-8-fluoroerythronolide b (**6**). Since fluorine is nearly isosteric with hydrogen,[2] its introduction at C-8 of the erythromycin aglycones should not give rise to significant conformational modifications in their structures. In a mutasynthetic experiment,[3] therefore, the new compounds might yield fluorinated macrolide antibiotics by deceiving the glyconsidating enzymes of *Streptomyces erythraeus* ATCC 31772, a blocked strain which we previously showed[4] to convert both erythronolides A and B to erythromycin A. The possible bioconversion products might have perculiar biological properties, as is reported to happen in a variety of molecules in which an atom of hydrogen is replaced by fluorine.[5]

At first we studied (Scheme 1) the fluorination of enol ether group present in 8,9-anhydro-erythronolide A and B 6,9-hemiketals (**1** and **2**)[1,6] with trifluoromethyl hypofluorite (CF_3OF), an electro-



1 R = OH
2 R = H

3 R = OH
4 R = H

5 R = OH
6 R = H

Scheme 1.

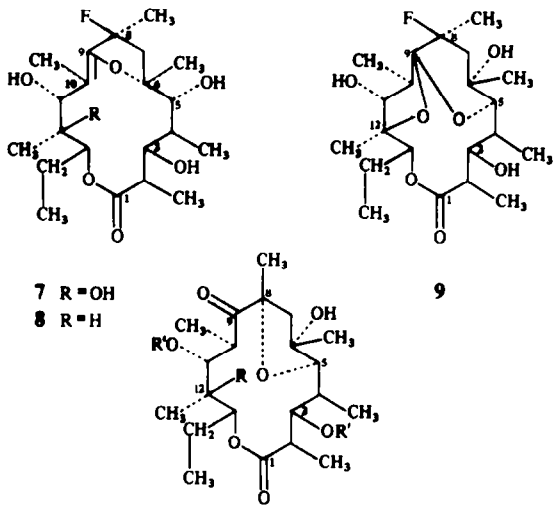
philic fluorinating agent previously employed for the introduction of a fluorine atom into naturally products.[7,8]

The fluorination of 8,9-anhydroerythronolide A 6,9-hemiketal (**1**) with CF_3OF (dichloromethane-Freon 11, 0.5 h, −80°),[9] in the presence of calcium oxide to neutralize hydrofluoric acid produced a 9:1 mixture of (8S)-8-fluoroerythronolide A 6,9;9,11-spiroketal (**3**) and (8S)-8-fluoroerythronolide A (**5**). The separation of the two products **3** and **5** was accomplished by column chromatography on silica gel. Spectral properties (^{1}H-NMR and UV) and microanalysis provided evidence for the structures assigned to these compounds. The ^{1}H-NMR spectra of **3** and **5** were compared with those of the known compounds erythronolide A 6,9;9,11-spiroketal[1] and erythronolide A.[10] The resonances associated with the protons at C-3, C-5 and C-11 were unchanged whereas those associated with the methyl group at C-6 and the protons at C-7 were modified only by the presence of the fluorine atom[11] at C-8. Compound **3** did not exhibit characteristic UV maxima. The UV spectrum of (8S)-8-fluoroerythronolide A (**5**) revealed a carbonyl absorption at 287 nm (ϵ 25), while the equivalent absorption of erythronolide A was at 285 nm (ϵ 52). As expected, the introduction of the equatorial fluorine atom at C-8 left the UV maximum unaffected.[12] This result was consistent with an 8-fluorine atom in **5** with the same stereochemistry as the C-8 hydrogen in erythronolide A.

The formation of the spiroketal **3** is likely to be due to an intramolecular nucleophilic interaction between the α-fluorocarbon ion at C-9 and the hydroxyl group at C-11. On the other hand, the presence of water coming from the reaction between calcium oxide and hydrofluoric acid, could account for the formation of (8S)-8-fluoroerythronolide A (**5**). In this case a nucleophilic interaction occurs between water and the fluoro-carbon ion. Similar pattern was observed when the analogous transformation of 8,9-anhydroerythronolide B 6,9-hemiketal (**2**) was performed. Both (8S)-8-fluoroerythronolide A (**5**) and (8S)-8-fluoroerythronolide B (**6**) exist exclusively as fluoroketones; fluoroketone-hemiketal tautomerism[13] was not observed in any tested solvent.

Conversion of **3** to (8S)-8-fluoroerythronolide A (**5**) showed that the absolute configuration at C-8 was identical for both products. An attempt to form (8S)-8-fluoroerythronolide A (**5**) from (8S)-8-fluoroerythronolide A 6,9;9,11-spiroketal (**3**) under conditions which readily convert 8-hydroxyerythromycin B 6,9;9,11-spiroketal in 8-hydroxyerythromycin B (acetic acid-water pH 3, reflux for 5 min)[14] recovered the starting product. When these conditions were slightly modified (acetic acid-water pH 2.5, reflux for 6 h), a multicomponent mixture was obtained. Besides (8S)-8-fluoroerythronolide A, the following compounds (Scheme 2) were isolated: 9,10-anhydro-(8S)-8-fluoroerythronolide A 6,9-hemiketal (**7**), (8S)-8-fluoroerythronolide A 5,9;9,12-spiroketal (**9**) and 5,8-epoxy-8-*epi*-erythronolide A (**10**).

In analogy to reported procedures,[1] compound **7** was also obtained by prolonged reflux of **3** in aqueous pyridine. The structure of 9,10-anhydro-(8S)-8-fluoroerythronolide A 6,9-hemiketal (**7**) was established by its NMR spectrum. The 9,10-double bond was indicated by the presence of an allylic-proton at δ



7 R = OH
8 R = H

9

10 R = OH, R' = H
11 R = R' = H
12 R = OH, R' = $COCH_3$
13 R = H, R' = $COCH_3$

Scheme 2.

5.60 ppm in the pyridine-d_5 solution spectrum of **7**. It appeared as a doublet due to its long-range coupling with the fluorine atom[11] at C-8. The remaining NMR parameters of **7** very closely corresponded to those of the known compound 9,10-anhydroerythronolide A 6,9-hemiketal[1] in every respect, including the chemical shifts of the protons at C-3 and C-5 as well as in the magnitude of their coupling constants.

Compound **9** did not exhibit UV maxima between 200 and 350 nm. Its IR spectrum and that previously reported for erythronolide A 5,9;9,12-spiroketal[1] were nearly identical. Also, ^{1}H-NMR spectra showed a close structural similarity between the two compounds.

The UV spectrum of **10** revealed a carbonyl absorption at 300 nm (ϵ 50) while the above mentioned equivalent absorption of erythronolide A was at 285 nm (ϵ 52). Compound **10** was converted into 3,11-O-diacetyl derivative **12** with acetic anhydride in pyridine.[15] Comparison of ^{1}H-NMR absorption at C-3, C-5 and C-11 protons of **10** and its corresponding diacetyl derivative **12** showed that the expected paramegnetic shift[16] on acetylation of the secondary hydroxyl groups occurred only for the protons at C-3 and C-11. In addition, the C-5 proton absorption of both **10** and **12** appeared as a doublet with the coupling constant $J_{4,5} = 9.5$ Hz, which was expected since Dreiding stereomodels indicated the dihedral angle between the C-5 and C-4 protons of **10** and **12** to be about 180°. These ^{1}H-NMR results together with the bathochromic UV shift[17] of the carbonyl absorption of **10** relative to erythronolide A, suggested that **10** arose from **5** as a consequence of the favoured axial attack of the C-5 hydroxyl group at C-8 with concomitant substitution of the fluorine atom and inversion of the methyl group. This has analogy in the kinetically controlled transannular 2,5-epoxidation of 2β-bromo-3α,5α-diolsteroids in aqueous acid.[18] Treatment of (8S)-8-fluoroerythrono-

lide B 6,9;9,11-spiroketal (**4**) with aqueous acetic acid under the conditions reported for **3**, gave an analogous range of products: (8S)-8-fluoroerythronolide B (**6**), 9,10-anhydro-(8S)-8-fluoroerythronolide B 6,9-hemiketal (**8**) and 5,8-epoxy-8-*epi*-erythronolide B (**11**).

In constrast to the erythronolides A and B, the corresponding fluorinated compounds **5** and **6** are stable in a mineral acid solution at pH 1.7 (Figs. 1 and 2). Analogous behaviour with consequent enhanced absorption could be therefore envisaged for possible new antibiotics derived from them, should the compounds **5** and **6** be successfully converted by mutasynthesis into erythromycin analogues.

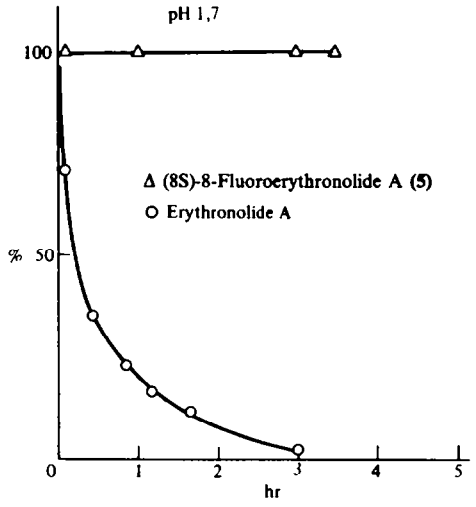


Fig. 1.

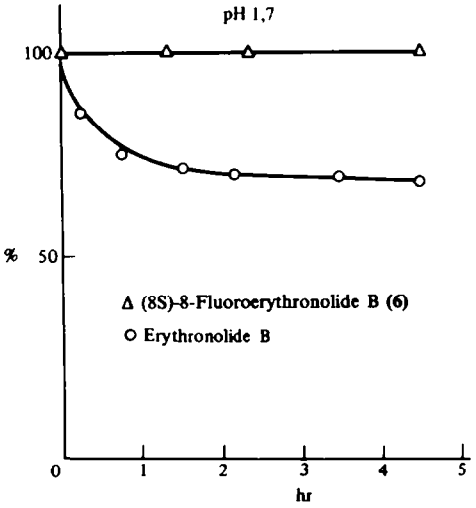


Fig. 2.

EXPERIMENTAL

Elemental analyses were performed by Alfred Bernhardt Microanalytical Laboratories, Elbach über Engelskirken, West Germany. All melting points were taken in open capillary tubes using a Tottoli apparatus (Büchi, Flawil, Switzerland) and are uncorrected. Optical rotations were determined at 20° in 1% methanol solutions with a Schmidt–Haentsch polarimeter. Ultraviolet (UV) spectra were measured in methanol using a Cary 210 spectrophotometer. Unless otherwise indicated, infrared (IR) spectra were obtained on a Perkin–Elmer 577 spectrophotometer for KBr discs (0.001 g of substance in 0.2 g of KBr). Proton nuclear magnetic resonance (^{1}H-NMR) spectra were obtained on a Varian T-60 A spectrometer at room temperature in pyridine-d_5 (C = 0.05 g/ml). Chemical shifts are reported in ppm from tetramethylsilane (TMS) as internal reference and coupling constants are reported in Hz.

High performance liquid chromatography (HPLC) analyses were carried out according to a modification of a described procedure.[19] A Hewlett–Packard 1084B liquid chromatograph equipped with a variable-wavelength detector at 210 nm and a Lichrosorb RP8 10 μ stainless steel column, 250 × 4.6 mm i.d., was used. Flow rate of the mobile phase was 2.0 ml/min and the column was operated at 40°. Mobile phase consisted of acetonitrile – 0.01 M phosphate buffer pH 7.0 (40:60, v/v).

Fluorination by CF_3OF of 8,9-*anhydroerythronolide A* 6,9-*hemiketal* (**1**)

A soln of CF_3OF in Freon 11 at −80° was prepared as follows: a CF_3OF excess (about 2 equiv) was dissolved in Freon 11 (previously cooled to −80°), by slowly adding the gas through a sparger, while the CF_3OF cylinder was continuously weighted. Its concentration was determined by iodometric titration (about $2.5 \cdot 10^{-3}$M). The soln of CF_3OF in Freon 11 was slowly added at −80° with stirring to a mixture of 4 g (0.010 mol) of 8,9-anhydroerythronolide A 6,9-hemiketal (**1**)[1] and calcium oxide (1.95 g) in Freon 11 (295 ml) and dichloromethane (370 ml). Progress of the reaction was periodically monitored by HPLC. After disappearance (or minimization) of the starting compound HPLC peak, stirring was continued for 5 min and nitrogen was bubbled through the soln to remove the CF_3OF excess at −80°. The soln was allowed to warm to room temp, washed with sat $NaHCO_3$ soln, then washed neutral with water and finally dried on anhydrous sodium sulfate. Removal of the solvent under reduced pressure afforded a crude product which was purified by silica gel column chromatography (ratio 1:50), prepared in dichloromethane–95% methanol (98:2, v/v). Elution with increasing concentrations of 95% methanol in dichloromethane first gave eluates containing only (8S)-8-fluoroerythronolide A 6,9;9,11spiroketal (**3**). These fractions were combined and evaporated under reduced pressure to yield, after crystallization from acetone–hexane, 3.4 of **3** m.p. 192–3°. (Found: C, 60.22; H, 8.51; F, 4.69. Calc for $C_{21}H_{35}FO_7$: C, 60.27; H, 8.43; F, 4.54%); $[\alpha]_D$ +64.7°; no UV maximum between 200 and 350 nm; IR 3560, 3420, 1720, 1460, 1395, 1380, 1355, 1345, 1330 cm^{-1}; ^{1}H-NMR δ 4.85 (d, 1, C-11 H, $J_{10,11}$ = 5) 4.20 (d, 1, C-5 H, $J_{4,5}$ = 1.5) 4.15 (dd, 1, C-3 H, $J_{2,3}$ = 10 and $J_{3,4}$ = 2).

Fractions containing only (8S)-8-fluoroerythronolide A (**5**) were combined and evaporated under reduced pressure to yield, after crystallization from acetone–hexane, 0.15 g of pure **5**, m.p. 239–40°. (Found: C, 57.87; H, 8.63; F, 4.19. Calc for $C_{21}H_{37}FO_8$: C, 57.78; H, 8.54; F, 4.35%); $[\alpha]_D$ −3.1°; UV 287 nm (ϵ 25.3); IR 3610, 3550, 3480 (shoulder), 3380 (shoulder), 1735, 1700, 1460, 1405, 1390, 1380, 1350, 1325 cm^{-1}; ^{1}H-NMR δ 4.65 (d, 1, C-11 H, $J_{10,11}$ = 1.5) 4.05 (dd, 1, C-3 H, $J_{2,2}$ = 10.5 and $J_{3,4}$ = 1.5) 3.90 (d, 1, C-5 H, $J_{4,5}$ = 2.5).

Fluorination by CF_3OF of 8,9-*anhydroerythronolide B* 6,9-*hemiketal* (**2**)

Following the above procedure for the preparation of **3** and **5**, 3.85 g (0.010 mol) of 8,9-anhydroerythronolide B 6,9-hemiketal (**2**)[6] yielded 3.9 g of a mixture of (8S)-8-fluoroerythronolide B 6,9;9,11-spiroketal (**4**) and (8S)-8-fluoroerythronolide B (**6**). Crystallization from acetone–hexane gave 3.45 g of **4**, m.p. 191–2°. (Found: C,

62.63; H, 8.82; F, 4.81. Calc for $C_{21}H_{35}FO_6$: C, 62.67; H, 8.76; F, 4.72%); $[\alpha]_D$ +42.6°; no UV maximum between 200 and 350 nm; IR 3540, 3450, 1735, 1460, 1260, 1170 cm^{-1}; ^{1}H-NMR δ 5.75 (broad s, 1, C–11 H) 4.25 (d, 1, C–H 5, $J_{4,5}$ = 1.5) 4.20 (dd, 1, C–3 H, $J_{2,3}$ = 10.5; $J_{3,4}$ = 2).

The mother liquors enriched in (8S)-8-fluoroerythronolide B (**6**) were purified by silica gel column chromatography (ratio 1:50). Elution with dichloromethane –95% methanol (98:2) yielded 0.075 g of **6**.

A sample was crystallized from acetone–hexane, m.p. 247–8°. (Found: C, 59.92; H, 9.00; F, 4.59. Calc for $C_{21}H_{37}FO_7$: C, 59.98; H, 8.87; F, 4.52%); $[\alpha]_D$ –30°; UV 286 nm (ϵ 26); IR 3540, 1727, 1705, 1460, 1330, 1270, 1175, 1130 cm^{-1}; ^{1}H-NMR δ 4.60 (dd, 1, C–H 11, $J_{10,11}$ = 2, $J_{11,12}$ = 10.5) 3.90 (dd, 1, C–H 3, $J_{2,3}$ = 10 and $J_{3,4}$ = 2) 3.85 (d, 1, C–H 5, $J_{4,5}$ = 1.5).

Preparation of (8*S*)-8-*fluoroerythronolide A* (**5**), 9,10-*anhydro*-(8*S*)-8-*fluoroerythronolide A* 6,9-*hemiketal* (**7**), (8*S*)-8-*fluoroerythronolide A* 5,9;9,12-*spiroketal* (**9**) *and* 5,8-*epoxy*-8-*epi*-*erythronolide A* (**10**) *by refluxing* (8*S*)-8-*fluoroerythronolide A* 6,9;9,11-*spiroketal* (**3**) *in aqueous acetic acid.*

A suspension of 6.275 g (0.015 mol) of (8S)-8-fluoroerythronolide A 6,9;9,11-spiroketal (**3**) in 4050 ml of aqueous acetic acid (pH 2.5) was refluxed at 110° under stirring. After 0.5 h at 110° all the starting material was dissolved. Heating was continued for 1 h and then the solution was cooled as rapidly as possible to room temp, neutralized with a sat $NaHCO_3$ soln and extracted with ethyl acetate. The ethyl acetate solution was dried on anhydrous sodium sulfate and evaporated to dryness under reduced pressure. The crude product was purified by column chromatography on silica gel (ratio 1:50) prepared with dichloromethane and eluted with increasing concentration of 95% methanol in dichloromethane. The first fractions contained only 9,10-anhydro-(8S)-8-fluoroerythronolide A 6,9-hemiketal (**7**). These were combined, evaporated under reduced pressure and crystallized from hexane to give 0.8 g of **7**: m.p. 166–7°. (Found: C, 60.41; H, 8.50; F, 4.35. Calc for $C_{21}H_{35}FO_7$: C, 60.27; H, 8.43; F, 4.54%); $[\alpha]_D$ +20°; IR 3480, 1720, 1460, 1390, 1315, 1265 (broad), 1210, 1190, 1155, 1120 cm^{-1}; ^{1}H-NMR δ 5.60 (d, 1, C–11 H, $J_{11,F}$ = 2.5). Later fractions, containing only 5,8-epoxy-8-*epi*-erythronolide A (**10**), were combined and evaporated under reduced pressure to yield 0.25 g of **10**. Crystallization from acetone–hexane gave needles, m.p. 217–8°. (Found: C, 60.66; H, 8.85. Calc for $C_{21}H_{36}O_8$: C, 60.55; H, 8.71%); $[\alpha]_D$ –79°; UV 300 nm (ϵ 50); IR 3620, 3560, 3510, 1740, 1695, 1465, 1380, 1345, 1225, 1170, 1130 cm^{-1}; ^{1}H-NMR δ 4.90 (d, 1, C–5 H, $J_{4,5}$ = 9.5). Final eluates, containing mixture of (8S)-8-fluoroerythronolide A (**5**) and (8S)-8-fluoroerythronolide A 5,9;9,12-spiroketal (**9**) were combined and evaporated to dryness under reduced pressure. By fractioned crystallization from acetone it was possible to separate 0.7 g of **5**, identical in all respects with that above prepared, and 0.35 g of analytically pure (8S)-8-fluoroerythronolide A 5,9;9,12-spiroketal (**9**): m.p. 260–1°. (Found: C, 60.35; H 8.54; F, 4.39. Calc for $C_{21}H_{35}FO_7$: C, 60.27; H, 8.43; F, 4.54%); $[\alpha]_D$ +33.7°; no UV maximum between 200 and 350 nm; IR 3560, 3470, 1745, 1465, 1390, 1380, 1340, 1305, 1180 (shoulder), 1160, 1130, 1105 cm^{-1}.

Preparation of (8S)-8-*fluoroerythronolide B* (**6**), 9,10-*anhydro*-(8S)-8-*fluoroerythronolide B* 6,9-*hemiketal* (**8**) *and* 5,8-*epoxy*-8-*epi*-*erythronolide B* (**11**) *by refluxing* (8S)-8-*fluoroerythronolide B* 6,9;9,11-*spiroketal* (**4**) *in aqueous acetic acid.*

Following the above procedure 6 g (0.015 mol) of (8S)-8-fluoroerythronolide B 6,9;9,11-spiroketal (**4**) was refluxed in aqueous acetic acid for 6 h to afford 5.9 g of yellow foam. Purification on silica gel (ratio 1:50), using dichloromethane–95% methanol (98:2) as eluent, and subsequent crystallization from acetone–hexane yielded 1.5 g of (8S)-8-fluoroerythronolide B (**6**), identical in all respects with that prepared above; 1.4 g of 9,10-anhydro-(8S)-8-fluoroerythronolide B 6,9-hemiketal (**8**): m.p. 195–6°. (Found: C, 62.56; H, 8.85; F, 4.87. Calc for $C_{21}H_{35}FO_6$: C, 62.67; H, 8.76; F, 4.72%); $[\alpha]_D$ –24.9°; IR 3470, 3400, 1700, 1470, 1420, 1390, 1380, 1320, 1275, 1210, 1155, 1135 cm^{-1}; ^{1}H-NMR δ 5.35 (dd, 1, C–11 H, $J_{11,12}$ = 10.5 and $J_{11,F}$ = 2.5); 0.3 g of 5,8-epoxy-8-*epi*-erythronolide B (**11**): m.p. 238–40°. (Found: C, 62.83; H, 9.04; Calc for $C_{21}H_{36}O_7$: C, 62.97; H, 9.06%); $[\alpha]_D$ –81.9; UV 298 nm (ϵ 66); IR ($CHCl_3$) 3600, 3500, 1710, 1455, 1380, 1330, 1175, 1120 cm^{-1}; ^{1}H-NMR δ 4.85 (d, 1, C–5 H, $J_{4,5}$ = 10).

3,11-*Di*-*O*-*acetyl*-5,8-*epoxy*-8-*epi*-*erythronolide A* (**12**)

A soln of 1.25 g (0.003 mol) of 5,8-epoxy-8-*epi*-erythronolide A (**10**) in 24 ml of anhydrous pyridine and 4.8 ml of acetic anhydride was heated on a steam bath for 16 h, then cooled and poured into 240 ml of ice–water. Chloroform extractions gave 1.5 g of an orange oil which was purified on silica gel (ratio 1:20) using dichloromethane–95% methanol (98:2) as eluent. The first fractions contained fast moving minor components and were discarded. Later fractions contained only 3,11-di-O-acetyl-5,8-epoxy-8-*epi*-erythronolide A (**12**). These fractions were combined and evaporated under reduced pressure to yield 1.3 g of pure **12** as a glass which resisted all attempts at crystallization. (Found: C, 60.12; H, 8.13. Calc for $C_{25}H_{40}O_{10}$: C, 59.98; H, 8.05%); ^{1}H-NMR δ 3.95 (d, 1, C–5 H, $J_{4,5}$ = 9.5).

3,11-*Di*-*O*-*acetyl*-5,8-*epoxy*-8-*epi*-*erythronolide B* (**13**).

Using the general procedure for the preparation of **12**, 1.2 g (0.003 mol) of 5,8-epoxy-8-*epi*-erythronolide B (**11**) were converted into 1.45 g of crude residue which was purified on silica gel (ratio 1:20), using dichloromethane–95% methanol (98:2) as eluent, and crystallized from hexane to give 1.2 g of 3,11-di-O-acetyl-5,8-epoxy-8-*epi*-erythronolide B (**13**): m.p. 163–4°. (Found: C, 62.15; H, 8.45. Calc for $C_{25}H_{40}O_9$: C, 61.96; H, 8.32%); $[\alpha]_D$ +6.6°; IR 3520, 1740, 1720, 1470, 1395, 1385, 1375, 1330, 1250, 1210, 1165, 1150, 1120 cm^{-1}; ^{1}H–NMR δ 3.80 (d, 1, C–5 H, $J_{4,5}$ = 10).

Preparation of 9,10-*anhydro*-(8S)-8-*fluoroerythronolide A* 6,9-*hemiketal* (**7**) *by prolonged reflux of* (8S)-8-*fluoroerythronolide A* 6,9;9,11-*spiroketal* (**3**) *in aq pyridine.*

A soln of 0.84 g (0.002 mol) of (8S)-8-fluoroerythronolide A 6,9;9,11-spiroketal (**3**) in 48 ml of pyridine and 32 ml of water was refluxed for 24 h. The aqueous solution was extracted with dichloromethane. Then the organic extract was washed with water, dried on anhydrous sodium sulfate and evaporated to dryness under reduced pressure. Crystallization of the crude residue (0.8 g) from hexane gave 0.6 g of 9,10-anhydro-(8S)-8-fluoroerythronolide A 6,9-hemiketal (**7**), identical in all respects with that prepared above.

Preparation of 9,10-*anhydro*-(8S)-8-*fluoroerythronolide B* 6,9-*hemiketal* (**8**) *by prolonged reflux of* (8S)-8-*fluoroerythronolide B* 6,9;9,11-*spiroketal* (**4**) *in aq pyridine.*

According to the above procedure for the preparation of **7**, 0.4 g (0.001 mol) of (8S)-8-fluoroerythronolide B 6,9;9,11-spiroketal (**4**) were converted to 0.4 g of yellow foam. Crystallization from acetone–hexane gave 0.25 g of 9,10-anhydro-(8S)-8-fluoroerythronolide B 6,9-hemiketal (**8**), identical in all respects with that prepared above.

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