Synthesis of C-2″β- and C-2″α-Fluoro Avermectin B_{1a}

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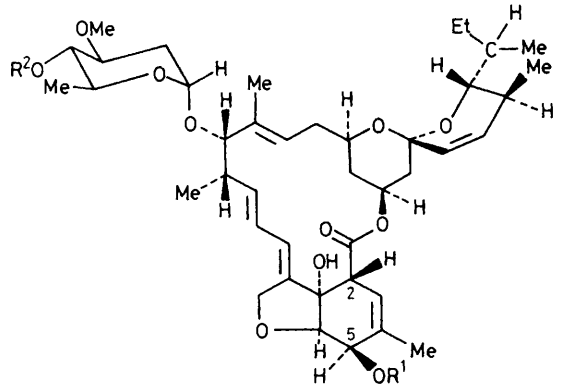
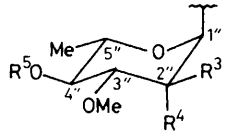
A synthesis of protected C-2β- and C-2α-fluoro oleandrosyl fluorides is presented; coupling of these carbohydrates with avermectin B_{1a} monosaccharide 5-*O*-t-butyldimethylsilyl derivative, followed by deprotection, furnished the title compounds whose biological activity was evaluated.

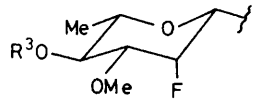
The avermectins constitute a group of eight closely related macrocyclic lactones with extremely potent antiparasitic activities.[1] Avermectin B_{1a} (**1**) is in development as an agricultural acaricide and insecticide. Structure–activity relationship studies[1] have shown that avermectin B_{1a} monosaccharide (**2**) has only about 25% and the aglycone alone about 5% of the biological activity of (**1**). These observations prompted us to undertake a programme aimed at further improving the biological activity of avermectin B_{1a} by modifying the environment of its glycosidic linkage between the two oleandrose units. In order to make this glycosidic linkage more resistant to hydrolysis, we prepared C-2″β- and C-2″α-fluoro avermectin B_{1a}, (**5a**) and (**5b**) respectively, and evaluated their biological activity.

Starting from L-rhamnose, benzyl 4-*O*-benzoyl-6-deoxy-3-*O*-methyl-α-L-mannopyranoside (**6**), a common protected





X

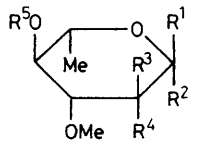


Y

(1) R^1 = H; R^2 = X with R^3 = R^4 = R^5 = H
(2) R^1 = R^2 = H
(3) R^1 = $SiMe_2Bu^t$; R^2 = H
(4a) R^1 = $SiMe_2Bu^t$; R^2 = X with R^3 = F; R^4 = H; R^5 = $SiMe_2Bu^t$
(4b) R^1 = $SiMe_2Bu^t$; R^2 = X with R^3 = H; R^4 = F; R^5 = $SiMe_2Bu^t$
(4c) R^1 = $SiMe_2Bu^t$; R^2 = Y with R^3 = $SiMe_2Bu^t$
(5a) R^1 = H; R^2 = X with R^3 = F; R^4 = R^5 = H
(5b) R^1 = H; R^2 = X with R^3 = R^5 = H; R^4 = F
(5c) R^1 = H; R^2 = Y with R^3 = H

synthetic intermediate of both C-2β- and C-2α-fluoro oleandrose, was prepared in an overall yield of 50%.[2] Hydrogenolysis of the benzyl group of (**6**) furnished (**7**) quantitatively. When the diol (**7**) was allowed to react at room temperature in tetrahydrofuran (THF) solution with 2.6 equiv. of diethylaminosulphur trifluoride (DAST)[3] a mixture was produced consisting of the readily separable and useful (**8**) (62%) and (**9**) (34%) which upon acid hydrolysis was recycled to starting material (**7**). In the conversion of (**7**) into (**8**) the intermediate β-L-mannopyranosyl fluoride system (**10**) was expected to be highly favourable for such an S_N2 process.[4] However, the α-L-mannopyranosyl fluoride structure (**9**) remains unchanged in the presence of DAST even at higher temperatures. Base catalysed debenzoylation of (**8**) followed by t-butyldimethylsilylation gave quantitatively the appropriately protected C-2β-fluoro oleandrose derivative (**11**), activated at its anomeric centre and ready for the glycosylation step.[5]

The preparation of a protected C-2α-fluoro oleandrose derivative was based on a recently discovered stereospecific 1,2-migration reaction in carbohydrate chemistry.[6,7] DAST treatment of (**6**) in boiling benzene furnished an anomeric mixture (80%) of 4-*O*-benzoyl-2-*O*-benzyl-6-deoxy-3-*O*-methyl-α-L- (**12**) and -β-L-glucopyranosyl fluoride (**13**). Hydrogenolysis of the benzyl group of this mixture was followed by the preparation of the trifluoromethanesulphonates (**14**) and (**15**) which could be readily separated. In the presence of $Bu_4N^+F^-$ or CsF, as expected,[4] fluorine introduction at C-2 on the β-L-glucopyranosyl fluoride system (**15**) proceeded better than on its α-L-counterpart (**14**) affording



(6) R^1 = OBzl; R^2 = R^3 = H; R^4 = OH; R^5 = Bz
(7) R^1, R^2 = H, OH; R^3 = H; R^4 = OH; R^5 = Bz
(8) R^1 = R^4 = H; R^2 = R^3 = F; R^5 = Bz
(9) R^1 = F; R^2 = R^3 = H; R^4 = OH; R^5 = Bz
(10) R^1 = R^3 = H; R^2 = F; R^4 = OH; R^5 = Bz
(11) R^1 = R^4 = H; R^2 = R^3 = F; R^5 = $SiMe_2Bu^t$
(12) R^1 = F; R^2 = R^4 = H; R^3 = OBzl; R^5 = Bz
(13) R^1 = R^4 = H; R^2 = F; R^3 = OBzl; R^5 = Bz
(14) R^1 = F; R^2 = R^4 = H; R^3 = OTf; R^5 = Bz
(15) R^1 = R^4 = H; R^2 = F; R^3 = OTf; R^5 = Bz
(16) R^1 = R^4 = F; R^2 = R^3 = H; R^5 = Bz
(17) R^1 = R^3 = H; R^2 = R^4 = F; R^5 = Bz
(18) R^1 = R^4 = F; R^2 = R^3 = H; R^5 = $SiMe_2Bu^t$
(19) R^1 = R^3 = H; R^2 = R^4 = F; R^5 = $SiMe_2Bu^t$

Bzl = $PhCH_2$–; Bz = Ph(C:O)–; Tf = CF_3SO_2–

respectively (**17**) (75%) and (**16**) (55%). Debenzoylation of (**16**) and (**17**) followed by t-butyldimethylsilylation gave quantitatively (**18**) and (**19**) respectively, ready for the glycosylation step.[5]

It is of interest to note the stability of C-1 fluoro-sugars in these and many other reactions which will be reported elsewhere.

In the presence of 1.5 equiv. of t-butyldimethylsilyl chloride, avermectin B_{1a} monosaccharide (**2**)[1] gave regiospecifically the 5-*O*-t-butyldimethylsilyl ether (**3**) (57%). Unreacted (**2**) (25%) could be also recovered. When a solution of (**3**) (1.15 mmol) in THF containing silver perchlorate, stannyl chloride, and molecular sieves was treated overnight in a nitrogen atmosphere, in the dark at +5 °C in three separate experiments with fluoro-sugars (**11**), (**18**), and (**19**) (1.24 mmol each), glycosylation products were obtained.[5] Using (**11**), C-2″β-fluoro avermectin B_{1a} 4″,5-bis-*O*-t-butyldimethylsilyl ether (**4a**) was produced (M^+ + H 1119) (18%). From (**18**) and (**19**), C-2″α-fluoro avermectin B_{1a} 4″,5-bis-*O*-t-butyldimethylsilyl ether (**4b**) (M^+ + H 1119) and the corresponding β-glycoside (**4c**) (M^+ + H 1119) were obtained after chromatographic separation. The glycosylation yield was about 20% and the ratio of (**4b**) to (**4c**) was 4 : 3 and 3 : 2 from respectively (**18**) and (**19**).

Structural proof for the glycosylation products was provided by their highly complex ^{13}C n.m.r. spectra. One-bond, geminal, and vicinal ^{13}C–^{19}F coupling constants[8] are in excellent agreement with the equatorial configuration of fluorine in (**4a**) and the axial orientation of fluorine in (**4b**) and (**4c**). The approximately identical chemical shift value of C-5″ in the spectrum of (**1**)[9] and (**4a**) (between δ 67.1 and 69.8) and (**4b**) (δ 69.8) fully supports the newly created glycosidic linkages as shown. In the spectrum of the β-glycoside (**4c**) the C-5″ resonance is strongly deshielded (δ 73.5) as expected.

Deprotection of the C-4″ and C-5 hydroxy groups of (**4a**), (**4b**), and (**4c**) with tetrabutylammonium fluoride, as described,[2] afforded (**5a**), (**5b**), and (**5c**) respectively, although in very moderate yields. This is presumably the result of the extreme sensitivity of the hydrogen atom at C-2 towards epimerisation under basic conditions.[10] However, both silyl ether groups could be removed in excellent yields (85%) with the hydrogen fluoride–pyridine complex[11] giving the corresponding deprotected avermectins.

The biological activity of (**5a**), (**5b**), and (**5c**) was compared with avermectin B_{1a} (**1**) in an *in vivo* anthelmintic assay and against the two-spotted spider mite. Both (**5a**) and (**1**) showed 100% activity against the two-spotted spider mite at 0.05 p.p.m. and both were active against gastrointestinal helminths at 0.00002% in the diet. Compound (**5b**) was slightly more active than (**1**) against helminths and ectoparasites. Interestingly, the β-glycoside (**5c**) was found to be 500 times less active against helminths but equally effective against the two-spotted spider mite.

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