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New potent insecticidal agent: 4′-fucosyl avermectin derivative

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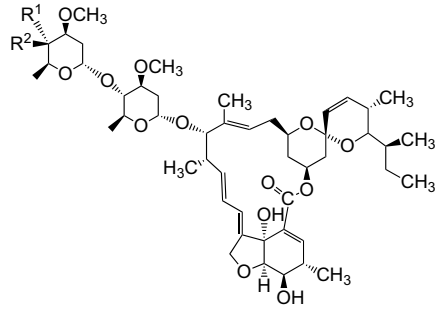
Abstract—A 4′-fucosyl avermectin derivative was designed and synthesized. This new avermectin derivative showed excellent in vivo bioactivity against cabbage larvae when compared to commercially available avermectin B_{1a}. In this synthesis, thioglycosyl donors, but not trichloroacetimidates, were found compatible with sugar-macrolide synthesis under rt promotion with NIS or I_2 in *N*-methylpyrrolidone.

The avermectins are a family of naturally occurring macrocyclic lactones with exceedingly high activity against helminthes and arthropods.[1] A primary fermentation product of *Streptomyces avermitilis*, avermectin B_{1a} (**1**, AVM, Fig. 1), is an important and widely used agricultural pesticide.[2] Although compound **1** is extremely effective against mites, it is much less effective against insects, especially the cabbage looper, the core earworm and the southern armyworm.[3] The level of activity against these species is insufficient to justify commercial development for these uses. Extensive investigation of the synthesis and biological evaluation of avermectin derivatives has been undertaken to obtain compounds with improved insecticidal activity.[4] From these efforts, a major breakthrough came with the discovery of 4″-aminoavermectins.[3a,5] These aminosugar-containing avermectins showed excellent activity against a variety of insect larvae, spider mites and aphids. The use of 4″-*epi*-(methylamino)-4″-deoxyavermectin B_{1a} benzoate (**2**, MK-244, Fig. 1) as an agriculture insecticide has achieved commercial success.[6] This specific example, when taken together with the success of other analogues,[7] demonstrates that synthetic modifications at the terminal sugar of AVM offers derivatives having potent and improved bioactivity.



1 R^1 = OH, R^2 = H
2 R^1 = H, R^2 = MeNH•HCO_2Ph

Figure 1. Structures of AVM (**1**) and MK-244 (**2**).

Our interest in these complex natural products led us to design a new AVM derivative in which 4′-hydroxyl of the oleandrosyl unit was replaced with a fully methylated α-L-fucopyranosyl moiety. L-Fucopyranosyl trichloroacetimidate donor **3** (Scheme 1) was selected for glycosylation of a modified avermectin lactone **4**[8] under TMSOTf promotion in anhydrous CH_2Cl_2 to synthesize this target. To our surprise, sluggish glycosylation results were obtained throughout a wide range of solvents and reaction temperatures.[9] Additional investigation showed that the macrolactone **4**, in the absence of donor, was highly unstable and decomposed quickly in the presence of catalytic amount of TMSOTf or 1 equiv of $BF_3{\cdot}Et_2O$ in CH_2Cl_2.

As most natural macrolide antibiotics contain sugar moieties,[10] it was important to investigate the general coupling reaction conditions for sugar donor and

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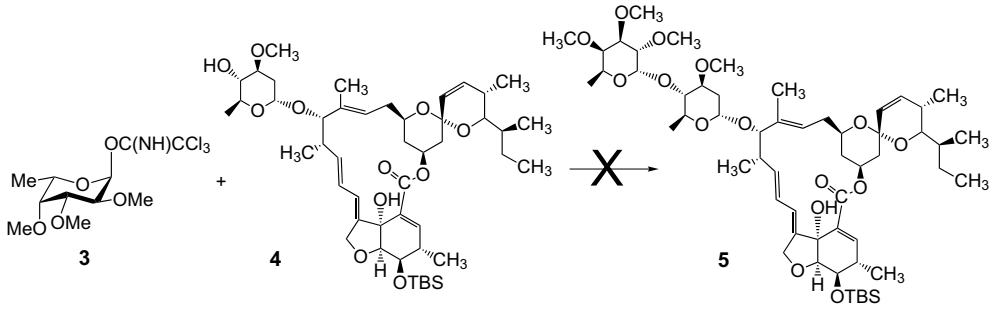

Scheme 1. Attempted synthesis of **5**.

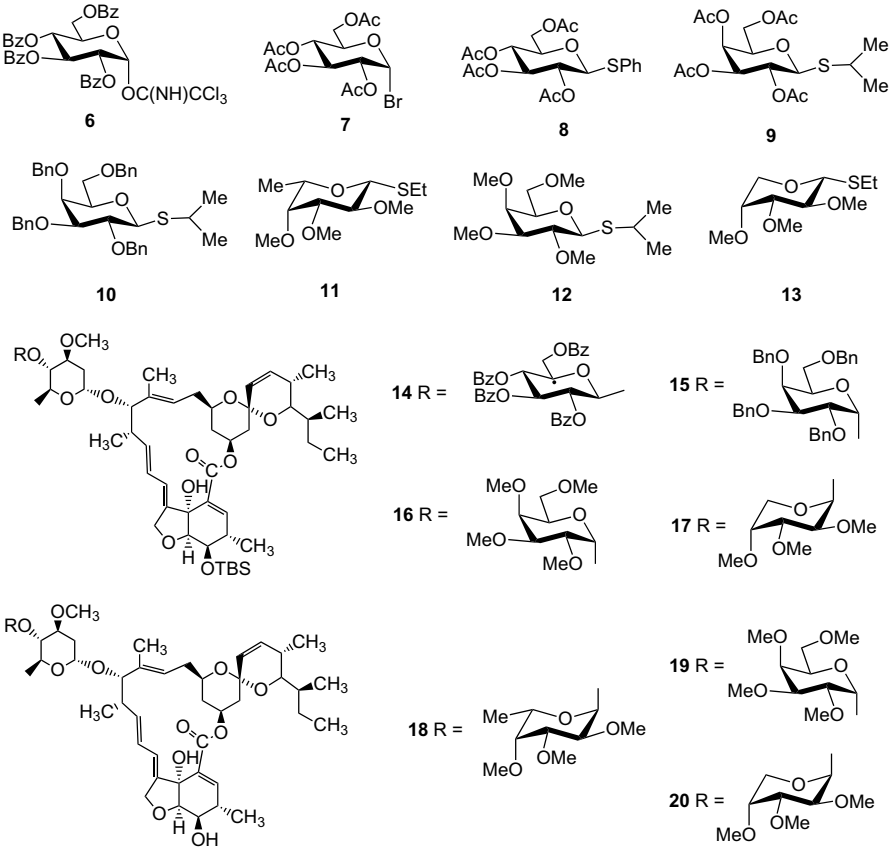

Figure 2. Glycosyl donors and products used in optimizing reaction conditions.

aglycone macrolactone. Thus, a number of glycosyl donors (Fig. 2) were prepared by routine methods and their reactive properties with lactone **4** were explored. AgOTf was a very compatible catalyst with trichloroacetimidate donor when compared to TMSOTf and $BF_3 \cdot Et_2O$.[11] AgOTf catalyzed glycosylation of glucopyranosyl trichloroacetimidate **6** and aglycon **4** in CH_2Cl_2 gave a very clean reaction with 91% yield of desired compound (see Table 1, entry 2). When the same reaction conditions were applied to the coupling of **3** and **4**, a 50% yield of expected **5** was isolated as an α,β mixture with a ratio of 1:1 (Table 1, entries 3 and 4). We speculated that the rapid consumption of **3** was a critical factor in this low yielding reaction. Unfortunately, changing solvent from CH_2Cl_2 to toluene and performing the reaction at the reduced temperature did not improve the yield. AgOTf, in the presence or absence of lutidine, failed to catalyze the glycosylation of lactone **4** with bromide donor **7** (entries 5 and 6).

Thioglycosides have often been applied in macrolide antibiotics synthesis.[12] However, when thioglycosides **8** and **9** were used under promotion with MeOTf, NBS or NIS catalysts, no desired products were obtained (entries 7–10). These results suggested that fully acetyl protected donor might be deactivated. When a benzylated thioglycoside donor **10** was used in the presence of NIS, a 60% yield of product was isolated as an α:β mixture (entry 11). Encouraged by these results, together with the observation that most sugar residues found in antibiotics are methylated and deoxygenated,[10] we prepared fucosyl thioglycoside donor **11** for the glycosyl-

Table 1. Glycosylation of sugar donor (**3**, **6**–**13**) and macrolactone **4**

Entry	Donor	Catalyst	Solvent	Result (isolated yield)
1	**3**	TMSOTf	CH_2Cl_2	No desired product
2	**6**	AgOTf	CH_2Cl_2	**14**, 91%, β only
3	**3**	AgOTf	CH_2Cl_2	**5**, 50%, α:β = 1:1
4	**3**	AgOTf	Toluene	**5**, 50%, α:β = 1:1
5	**7**	AgOTf	CH_2Cl_2	No desired product
6	**7**	AgOTf/lutidine	CH_2Cl_2	No desired product
7	**8**	MeOTf	CH_2Cl_2	No desired product
8	**8**	NBS	CH_2Cl_2	No desired product
9	**9**	NBS	CH_2Cl_2	No desired product
10	**9**	NIS	*N*-Methylpyrrolidone	No desired product
11	**10**	NIS	CH_2Cl_2	**15**, 60%, α:β = 1:1
12	**11**	NIS	CH_2Cl_2	**5**, 45%, α:β = 1:1
13	**10**	NIS	*N*-Methylpyrrolidone	**15**, 70%, α:β = 2:1
14	**11**	NIS	*N*-Methylpyrrolidone	**5**, 86%, α:β = 4:1
15	**11**	I_2	*N*-Methylpyrrolidone	**5**, 82%, α:β = 4:1
16	**12**	I_2	*N*-Methylpyrrolidone	**16**, 80%, α:β = 7:3
17	**13**	I_2	*N*-Methylpyrrolidone	**17**, 85%, α:β = 3:1

ation of **4** under the same reaction conditions, and a 45% yield of desired product was obtained as a 1:1 α:β mixture (entry 12). Further investigation showed that both **10** and **11** could afford improved yields and stereo-selectivities in *N*-methylpyrrolidone (entries 13 and 14). A typical procedure is the following: To a solution of **11** (1 mmol) and **4** (0.9 mmol) in *N*-methylpyrrolidone (5 mL) was added NIS (1.1 equiv) under a N_2 atmosphere. The mixture was stirred at 25 °C for 1 h, then poured into water and extracted with CH_2Cl_2. A routine column separation gave α-linked **5** (86% total yield, α,β = 4:1) as an amorphous solid.

We next examined I_2 as a less expensive replacement for NIS, to lower the cost of making this potential pesticide, and found I_2 to be a suitable promoter for this reaction.[13] When methylated glycosyl donors **11**, **12** and **13** were coupled with **4** in *N*-methylpyrrolidone under I_2 promotion, compounds **5**, **16** and **17** were afforded predominantly as the α-isomers in 82%, 80% and 85% yield, respectively.[14] Finally, clean removal of the *tert*-butyldimethylsilyl (TBS) group from **5**, **16** and **17**, using hydrogen fluoride–pyridine complex, afforded the corresponding **18**, **19** and **20**, respectively. It is noteworthy that all attempts to cleave TBS with *tetra-n*-butylammonium fluoride, using published methods, failed.[15]

Bioactivity was evaluated in preliminary studies using the cabbage leaf dip bioassay described by Zhao et al.[16] The fourth instar larvae were tested with compounds **18**, **19** and **20** in acetone solution and mortality was assessed 3 days after treatment. The results showed potency at microgram levels as summarized in Table 2. Toxicity in animals was examined in ICR mice using standard methods and the LD_{50} of compound **18** was 87.5 mg/kg.

In conclusion, a novel AVM analogue has been designed and synthesized. The key step is the stereoselective high yielding glycosylation of 4′-position of AVM derivative. The use of fully methylated thioglycosides as donors, and NIS or I_2 as catalyst in *N*-methylpyrrolidone at rt, provided good yields of target AVM analogues, which show excellent bioactivity against cabbage larvae. The method described here should be valuable in the synthesis of other sugar-containing macrolide antibiotics.[10]

Table 2. Bioactivities of compounds **18**, **19**, **20** to cabbage larvae

Dosage	Microgram per larva	Total number	Dead number	Mortality (%)
18	2.0	90	84	93.3
19	2.0	90	77	85.5
20	2.0	90	68	75.5
1	2.0	90	48	53.3
2	2.0	90	83	92.2
Acetone	—	30	2	6.7

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14. Physical data for compound **17**: $[\alpha]_D^{25}$ −52 (*c* 1, $CHCl_3$); ^1H NMR: (400 MHz, $CDCl_3$): 0.85–0.95 (m, 10H, CH_3-28, CH_3-26a, CH_3-14a, H-18a), 1.14 (d, 3H, CH_3-12a), 1.24–1.26 (m, 6H, CH_3-6^I, CH_3-6^{II}), 1.45–1.50 (m, 4H, CH_3-14a, H-20a), 1.58–1.64 (m, 4H, H-16a, H-2^Ia, CH_2-27), 1.76 (m, 1H, H-18e), 1.88 (br s, 3H, CH_3-4a), 2.00–2.05 (m, 1H, H-20e), 2.23–2.29 (m, 4H, H-2^Ie, H-24, H-26, H-16e), 2.35–2.37 (d, 1H, 5-OH), 2.47–2.53 (m, 1H, H-12), 3.28–3.30 (m, 1H, H-2), 3.35–3.41 (m, 1H, H-4^I), 3.42 (s, 3H, OCH_3), 3.46–3.50 (m, 2H, H-3^{II}, H-25), 3.53–3.60 (3 s, 9H, OCH_3), 3.62–3.66 (dd, 1H, $J_{1,2}^{II,II}$ 4.1, $J_{3,2}^{II,II}$ 10.1 Hz, H-2^{II}), 3.78–4.00 (m, 7H, H-3^I, H-17, H-13, H-5^I, H-4^{II}, H-6, 7-OH), 4.20–4.23 (m, 1H, H-5^{II}), 4.28–4.32 (t, 1H, H-5), 4.68–4.74 (m, 3H, CH_2-8a, H-1^I), 4.96 (m, 1H, H-3), 5.37–5.43 (m, 2H, H-19, H-15), 5.54–5.57 (dd, 1H, $J_{23,22}$ 2.5, $J_{23,24}$ 9.9 Hz, H-23), 5.60 (d, 1H, $J_{1,2}^{II,II}$ 4.0 Hz, H-1^{II}), 5.70–5.72 (t, 2H, H-10, H-11), 5.75–5.78 (dd, 1H, H-22), 5.85–5.88 (m, 1H, H-9); ^{13}C NMR (100 MHz, $CDCl_3$): 12.02 (C-28), 12.96 (C-26a), 15.07 (C-14a), 16.38 (C-24a), 16.47 (C-6^{II}), 18.50 (C-6^I), 19.97 (C-4a), 20.00 (C-12a), 27.50 (C-27), 30.58 (C-24), 34.26 (C-16), 34.50 (C-26), 35.17 (C-2^I), 36.60 (C-18), 39.83 (C-12), 40.49 (C-20), 45.72 (C-2), 56.07, 57.99, 58.87, 61.70, 66.51 (C-5^I), 66.97 (C-5^{II}), 66.74 (C-5), 68.15 (C-19), 68.33 (C-8a), 68.48 (C-17), 74.89 (C-25), 77.62 (C-2^{II}), 79.02 (C-3^I), 79.05 (C-4^{II}), 79.25 (C-4^I), 79.26 (C-6), 80.11 (C-3^{II}), 80.41 (C-7), 82.57 (C-13), 95.31 (C-1^I), 95.77 (C-21), 96.96 (C-1^{II}), 118.06 (C-15), 118.37 (C-3), 120.43 (C-9), 124.76 (C-10), 127.78 (C-23), 135.31 (C-14), 136.30 (C-22), 137.98 (C-4), 138.04 (C-11), 139.59(C-8), 173.72 (C-1); MALDITOF-MS: calcd for $C_{50}H_{76}O_{15}$, 916.5 [M]; found: 939.70 $[M+Na]^+$; 955.70 $[M+K]^+$.
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