Chinese Chemical Letters Vol. 15, No. 7, pp 765-767, 2004
http://www.imm.ac.cn/journal/ccl.html

Synthesis of New 13-*O*-Acylavermectin B1 Aglycones

Qing An WU, Zhen Yuan XU*, Mei ZHENG, Dan Qian XU, Jun XU, Yin Chu SHEN

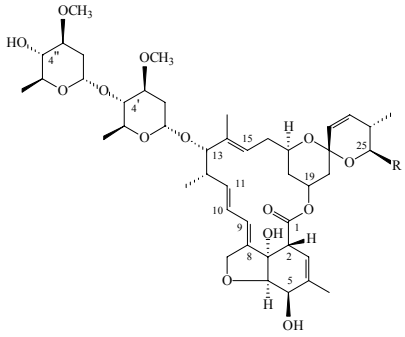
College of Chemical Engineering and Materials, Zhejiang University of Technology, Hangzhou 310032

Abstract: Six new 13-*O*-acylavermectin B1 aglycones(**3~8**) were synthesized from avermectin B1 aglycone and their bioactivities were evaluated against *Spodoptera exigua*, *Spodoptera eridania, Tetranychus urticae* and *Aphis fabae*.

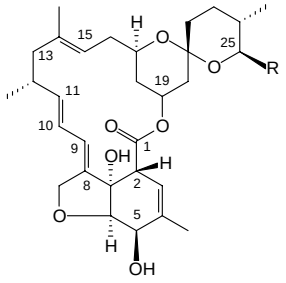
Keywords: 13-*O*-Acylavermectin B1 aglycone, synthesis, insecticidal and acaricidal activity.

The avermectins and the milbemycins, 16-membered macrocyclic lantones produced by *Streptomyces avermitilis* or *Streptomyces hygroscopicus*, respectively, are potent insecticidal, acaricidal and anthelmintic compounds[1, 2]. Removal of the 13α-dioleandrosyl substituent from the avermectins gives avermectin aglycones which are closely related to certain milbemycins (**Figure 1**). The major structural difference between the avermectin aglycones and the milbemycins is that the former have a hydroxyl substituent at the C-13 position, while the latter are unsubstituted at that position. Therefore, it has been paid much attention to modify at the C-13 position of the avermectin aglycones in

Figure 1 The structures of avermectin B1 and milbemycins



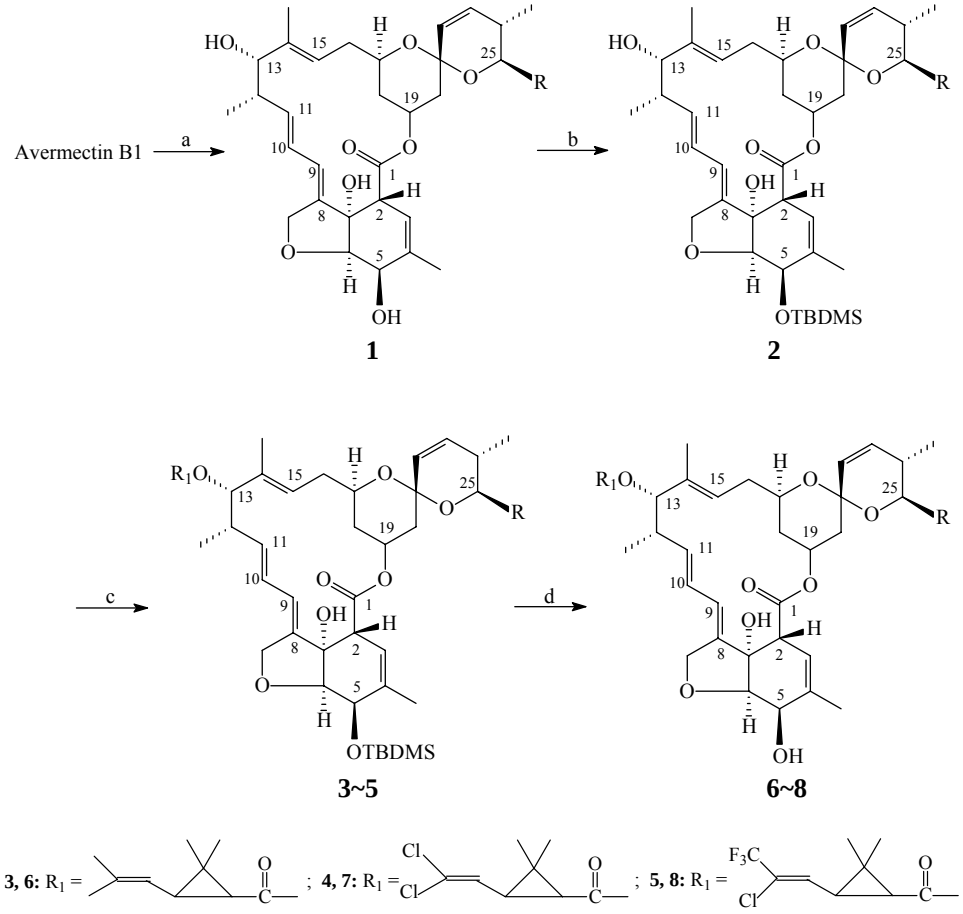
Avermectin B1
Avermectin B1a (R = *s*-butyl)
Avermectin B1b (R = *i*-propyl)



Milbemycins
Milbemycin α_1 (R = methyl)
Milbemycin α_3 (R = ethyl)
Milbemycin D (R = *i*-propyl)order

* E-mail: greenchem@zjut.edu.cn

Scheme 1



Reagents and conditions: (a) 10% H_2SO_4, THF-H_2O, 20ºC, 24h, 50.2%; (b) TBDMS-Cl, imidazole, THF, 25ºC, 6h, 81.3%; (c) DMAP, DIPEA, chrysanthemyl chloride/ **3**, dichlorochrysanthemyl chloride/ **4**, trifluoromethylchlorochrysanthemyl chloride/ **5**, CH_2Cl_2, 20ºC, 24h, **3**, 95.4%, **4**, 97.5%, **5**, 96.8%; (d) *p*-toluenesulfonic acid monohydrate, MeOH, 20ºC, 30min, **6**, 61.3%, **7**, 63.6%, **8**, 62.0%.

order to improve the bioactivity and reduce the toxicity of the precursor[3, 4]. Here we describe the synthesis of six new 13-*O*-acylavermectin B1 aglycones(**3~8**) by acylating avermectin B1 aglycone with chrysanthemyl chloride and halogen-containing chrysanthemyl chlorides (**Scheme 1**). The insecticidal and acaricidal activities of six new compounds (**3~8**) were preliminarily tested.

Avermectin B1 aglycone (compound **1**) was obtained by hydrolysis of avermectin B1 (containing 93.2% B1a and 3.5% B1b) with 10% H_2SO_4 in THF-H_2O in 50.2% yield[5]. Before the C-13 position hydroxyl group of **1** was acylated, the more reactive C-5 position hydroxyl group was selectively protected with *tert*-butydimethylsilyl (TBDMS) chloride in imidazole and THF to give compound **2** in 81.3% yield[4]. In the presence of

4-(dimethylamino) pyridine (DMAP) and N,N-diisopropylethylamine (DIPEA), **2** was then acylated with chrysanthemyl chloride, dichlorochrysanthemyl chloride and trifluoromethylchlorochrysanthemyl chloride, respectively, in CH_2Cl_2 to afford compounds **3~5** in 95.4~97.4% yields. Finally, the C-5 position protecting groups of **3**~**5** were removed with *p*-toluenesulfonic acid monohydrate in MeOH to give compounds **6~8** respectively in 61.2~63.6% yields. The structures of compounds **1~8** were confirmed by IR, MS and ^{1}H-NMR spectra[6].

The insecticidal and acaricidal activities of compounds **1~8** were tested against *Spodoptera exigua*, *Spodoptera eridania*, *Tetranychus urticae* and *Aphis fabae*. It was found that compounds **3~5** suffered a substantial loss of activity, however, compounds **6~8** exhibited higher activities than the parent compound **1**.

References and Note

1. G. Albers-Schonberg, B. H. Arison, J. C. Chabala, *et al*., *J. Am. Chem. Soc*., **1981**, *103*, 4216.
2. H. G. Davies, R. H. Green, *Chem. Soc. Rev*., **1991**, *20*, 211.
3. H. Mrozik, B. O. Linn, P. Eskola, *et al*., *J. Med. Chem*., **1989**, *32*, 375.
4. T. A. Blizzard, G. M. Margiatto, H. Mrozik, *et al*., *J. Med. Chem*., **1992**, *35*, 3873.
5. H. Mrozik, P. Eskola, B. H. Arison, *et al*., *J. Org. Chem*., **1982**, *47*, 489.
6. The data of IR, MS and ^{1}H-NMR were submitted to the editorial office of *CCL*.

Received 19 June, 2003