

天维菌素酰化衍生物的合成及杀虫杀螨活性

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摘要: 以天维菌素 B、天维菌素 B 单糖苷和天维菌素 B 苷元为原料, 经选择性 C-5 羟基保护, 在 C-13、C-4' 和 C-4'' 位引入不同酰基基团, 合成了 3 个系列共 23 个天维菌素 B 酰化衍生物, 并通过 ¹H NMR、¹³C NMR 和高分辨质谱对所有目标化合物的结构进行了表征。生物活性测定结果表明, 所有衍生物对小菜蛾 *Plutella xylostella*、朱砂叶螨 *Tetranychus cinnabarinus* 以及松材线虫 *Bursaphelenchus xylophilus* 均表现出不同程度的毒杀活性, 其中天维菌素 B 4'' 位衍生物的活性优于 4' 位衍生物及 13 位衍生物。化合物 **8e** 对小菜蛾和松材线虫的毒杀活性最优, LC₅₀ 值分别为 9.2 mg/L 和 0.42 mg/L, 化合物 **8b** 对朱砂叶螨的毒性最高, LC₅₀ 值为 0.0019 mg/L, 均优于对照药天维菌素 B。

关键词: 天维菌素 B; 酰化衍生物; 合成; 杀虫活性; 杀螨活性

中图分类号: TQ458.1; S482.3; S482.5 文献标志码: A

Synthesis, insecticidal and acaricidal activities of tenvermectin acylated derivatives

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Abstract: The derivatives of tenvermectin B, tenvermectin B monosaccharide and tenvermectin B aglycone were synthesized by introducing different acyl groups at the C-13, C-4' and C-4'' sites after the selective protection of C-5 hydroxyl group. All target compounds were characterized by ¹H NMR, ¹³C NMR and high resolution mass spectra. Their insecticidal activities were tested against *Plutella xylostella*, *Tetranychus cinnabarinus* and *Bursaphelenchus xylophilus*. All the tested compounds showed significant insecticidal activities against the above mentioned three insect species and the 4''-tenvermectin B derivatives were superior to the 4'- and 13-derivatives of tenvermectin B. Compound **8e** displayed potent activity to *P. xylostella* and *B. xylophilus* with LC₅₀ values of 9.2 mg/L and 0.42 mg/L,

收稿日期: 2019-06-16; 录用日期: 2019-09-06.

基金项目: 国家自然科学基金项目 (31471809); 中国博士后科学基金 (2018M630689).

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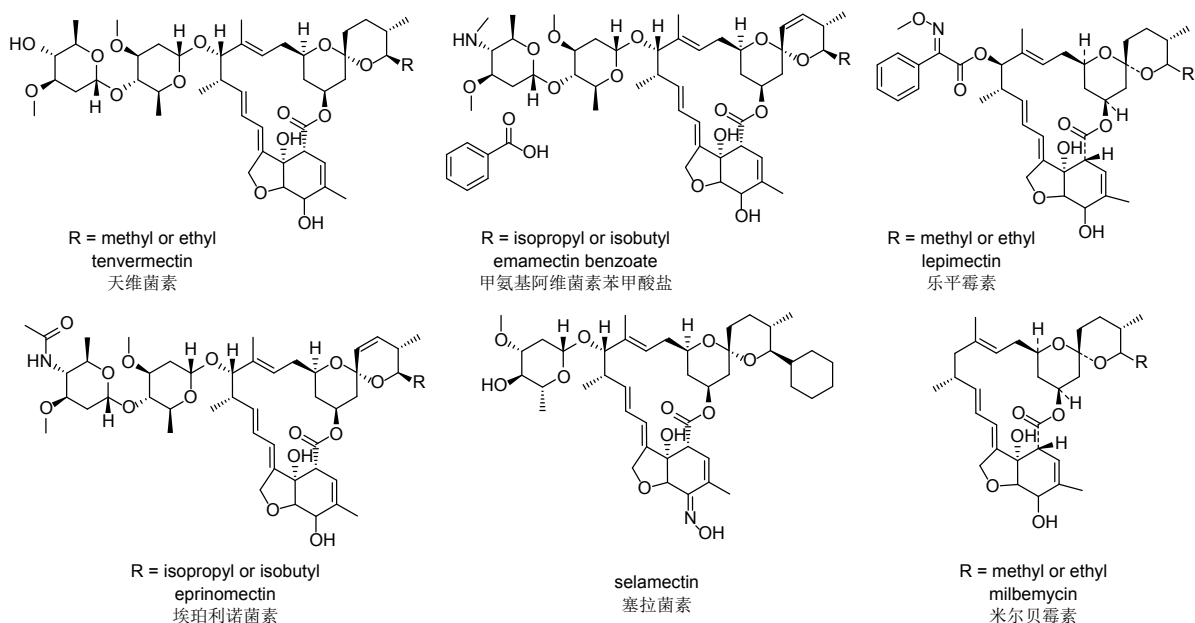
respectively. Moreover, compound **8b** showed the best inhibitory activity against *T. cinnabarinus* with LC₅₀ value of 0.0019 mg/L, which was superior to that of tenvermectin B.

Keywords: tenvermectin B; acylation derivatives; synthesis; insecticidal activity; acaricidal activity

天维菌素 (tenvermectin) 是对阿维菌素产生菌和米尔贝霉素产生菌的相关基因进行改造而构建的新的工程菌 *Streptomyces avermitilis* MHJ1101, 经发酵分离得到的一类活性更优、毒性更低, 并具有自主知识产权的新型十六元大环内酯化合物^[1]。与阿维菌素相比, 螺缩酮基团上 C22 和 C23 位双键饱和, C25 位由甲基或乙基取代; 与米尔贝霉素相比, C13 由 2 个齐墩果糖取代。本课题组先后在其产生菌发酵液中分离出系列天维菌素类似物^[2-6]。生物活性测定结果表明, 天维菌素类化合物对朱砂叶螨、小菜蛾、黏虫和松材线虫等表现出比同类化合物更为优异的活性, 而其毒性比阿

维菌素更低^[7-8], 具有较高的开发价值。

近年来, 除通过生物技术手段来提高该类十六元大环内酯化合物的活性外, 在其母体结构上进行化学结构优化来开发活性优、安全性更高的新品种, 也是该类化合物创制的重要途径^[9]。目前, 在化合物 C-13、C-4' 和 C-4'' 位点的修饰较为成功^[10], 其中包括: 对鳞翅目活性更优的甲氨基阿维菌素苯甲酸盐 (emamectin benzoate)^[11]; 对动物体内寄生线虫活性更好, 残留更低的埃珀利诺菌素 (epinomectin)^[12] 及塞拉菌素 (selamectin)^[13]; 速效性更好, 且与阿维菌素无交互抗性的乐平霉素 (lepimectin)^[14](图式 1)。



图式 1 米尔贝霉素及阿维菌素衍生物的结构式

Scheme 1 Structural formula of milbemycin and abamectin derivatives

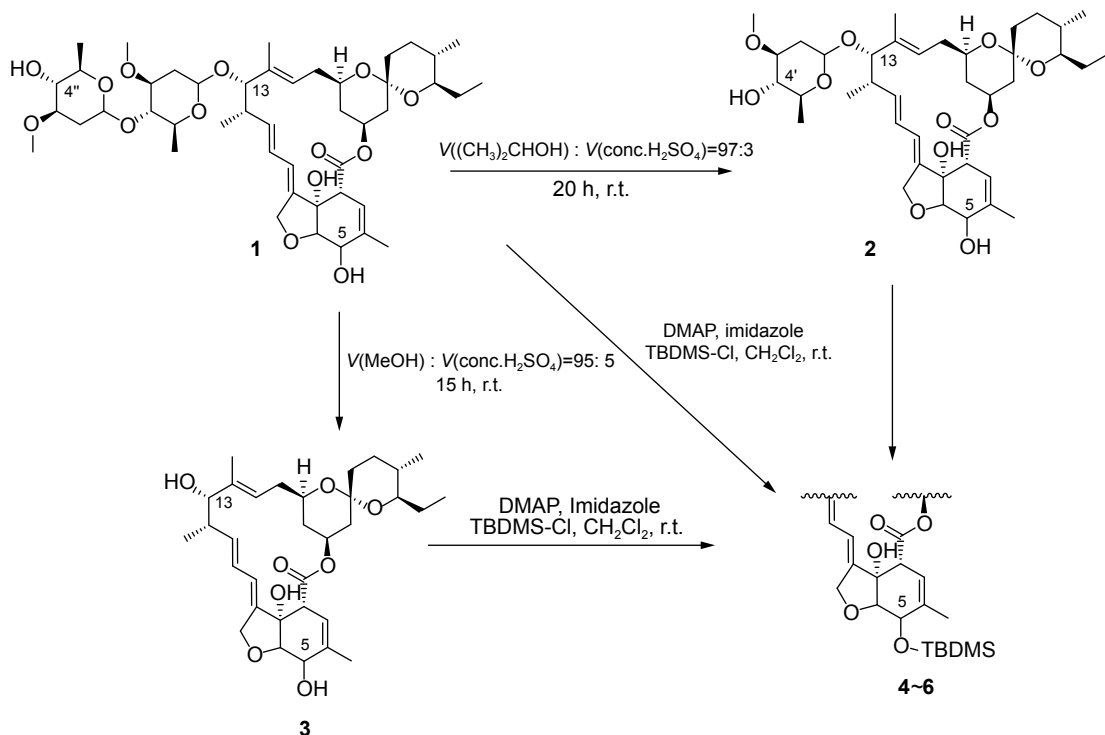
这些衍生物克服了原有化合物理化性质的不足, 改善了防治范围及防治效果。构效关系研究表明, 该类化合物 13 α -L-齐墩果糖基对生物活性的影响至关重要^[15-16]。鉴于此, 笔者采用活性官能团拼接策略, 对天维菌素 B 进行脱糖基后对 C-5 羟基进行保护 (图式 2), 并对其保护后的类似物在 C-4''、C-4' 和 C-13 位进行酰化修饰 (图式 3), 合成了 3 个系列天维菌素 B 酰化衍生物 (**8a**~**8j**,

9a~**9h** 和 **10a**~**10e**), 通过 ¹H NMR、¹³C NMR 和高分辨质谱对所有目标化合物的结构进行了表征, 并进行了杀虫、杀螨活性测定, 以期得到活性更好、杀虫谱更广的新化合物。

1 实验部分

1.1 仪器与试剂

YB102 万分之一电子天平, 上海海康电子仪



图式 2 中间体 2~6 的合成路线

Scheme 2 Synthesis routes of intermediates 2-6

器厂; DF-101S 恒温磁力搅拌器, 上海积坤化工科技有限公司; Digital water bath SB-1000 旋转蒸发仪, 日本 EYELA 公司; X-5 显微熔点测定仪 (温度未经校正), 巩义市予华仪器有限责任公司; Bruker AVANCE-400 超导核磁共振仪, Bruker, 德国; Shimadzu LC-8A 高效液相色谱制备仪 (Shimadzu-C18, 5 μ m, 20 mm \times 250 mm i.d), Shimadzu, Kyoto, 日本; Q-TOF Micro-LC-MS-MS mass spectrometer 高分辨质谱仪, Waters, 美国。

95% 天维菌素 B (1) 原药, 由浙江海正药业股份有限公司提供; 柱层析硅胶为 H 型 (48~75 μ m), GF₂₅₄ 薄层层析硅胶板 (TLC), 青岛海洋化工厂; 其他所有试剂为分析纯或色谱纯。

1.2 天维菌素 B 衍生物的合成

1.2.1 天维菌素 B 单糖苷 (2) 和天维菌素 B 苷元 (3) 的合成 参考文献 [15] 的方法合成, 得到天维菌素 B 单糖苷 (2), 白色泡状固体, 收率 93%, ESI-MS, m/z : 701.41[M-H]⁻; 天维菌素 B 苷元 (3), 淡黄色泡状固体, 收率 95%, ESI-MS, m/z : 557.31[M-H]⁻。

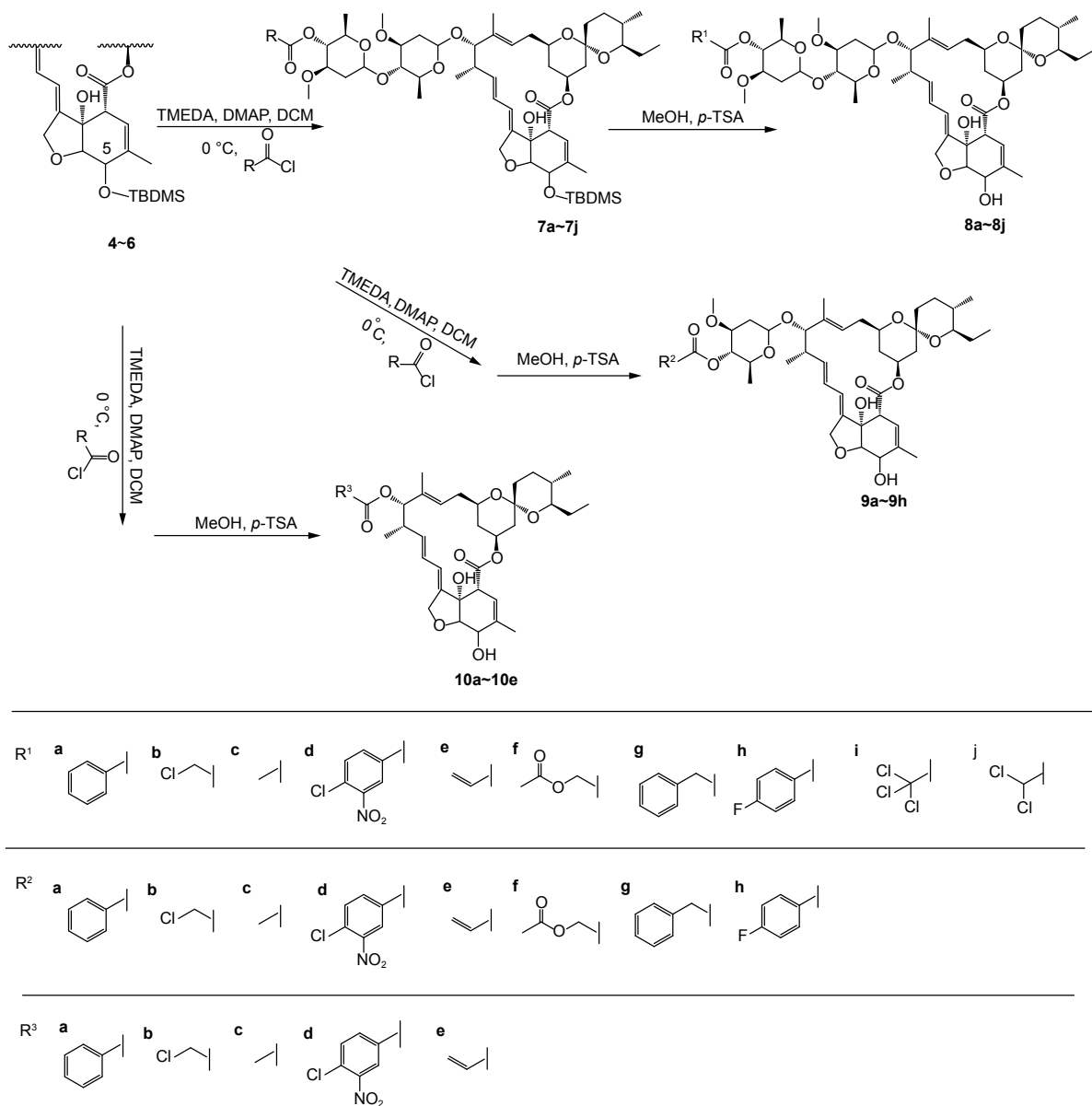
1.2.2 中间体化合物 4~6 的合成 参考文献 [17] 的方法合成, 得到 5-TBDMS-天维菌素 B (4), 白色泡沫状固体, 收率 95%, ESI-MS, m/z : 961.43[M+H]⁺; 5-TBDMS-天维菌素 B 单糖苷 (5), ESI-

MS, m/z : 839.51[M+Na]⁺, 白色固体, 产率 94%; 得 5-TBDMS-天维菌素 B 苷元 (6), 白色固体, 产率 95%, ESI-MS, m/z : 695.40 [M+Na]⁺。

1.2.3 目标化合物天维菌素 B 衍生物的合成

1.2.3.1 4''-O-酰基天维菌素 B 衍生物 (8a-8j) 合成通法 参考文献 [17] 的方法合成。将 1.06 mmol 化合物 4 加入 20 mL 二氯甲烷中, 搅拌溶解, 依次加入 2.12 mmol 四甲基乙二胺 (TMEDA) 和 0.11 mmol DMAP, 冰浴条件下缓慢滴加 1.8 mmol 不同取代的酰氯试剂 (a~j, 图式 3), 约 10 min 滴毕。保温反应 0.5~2 h, TLC (V (石油醚) : V (乙酸乙酯) = 1 : 1) 监测至反应完毕, 加入 1% 的盐酸水溶液 20 mL 淬灭反应, 搅拌 5 min, 静置分层, 二氯甲烷萃取 (3 \times 20 mL), 合并有机层, 依次加入饱和碳酸氢钠水溶液 (20 mL)、水 (20 mL) 和饱和食盐水 (20 mL) 洗涤, 无水硫酸钠干燥, 过滤, 滤液浓缩至干, 得中间体化合物 7a~7j。

将化合物 7a~7j 溶于 20 mL 甲醇中, 加入 0.4 g 对甲苯磺酸 (p -TSA), 室温搅拌 15 min, TLC (V (石油醚) : V (乙酸乙酯) = 1 : 1) 检测至反应完毕。用饱和碳酸氢钠中和, 二氯甲烷萃取 (3 \times 20 mL), 合并有机层, 无水硫酸钠干燥, 过滤, 滤液浓缩至干后经硅胶柱层析 [V (石油醚) : V (乙酸乙酯) =



图式 3 目标化合物 8a~8j、9a~9h 和 10a~10e 的合成路线
Scheme 3 Synthetic routes of compounds 8a-8j, 9a-9h and 10a-10e

4 : 1] 或高效液相色谱制备仪 (Shimadzu LC-8A, Shimadzu-C₁₈, 5 μm, 20 mm × 250 mm (i.d), λ = 243 nm, V = 20 mL/min, V(甲醇): V(水)=9 : 1), 纯化得产物 8a~8j。

8a: 4''-O-苯甲酰基天维菌素 B。收率 85%, 白色粉末; m.p. 155.5~159.4 °C; ¹H NMR (400 MHz, CDCl₃), δ: 0.84~0.89 (m, 4H, H-30, H-18a), 1.00 (t, J = 6.8 Hz, 3H, H-32), 1.20~1.43 (m, 12H, H-28, H-6', H-6'', H-24, H-31a, H-20a), 1.53~1.64 (m, 8H, H-29, H-22a, H-23, H-2''a, H-2'a), 1.69~1.79 (m, 3H, H-22b, H-31b, H-18b), 1.89 (br s, 3H, H-26), 2.01 (dd, J = 11.9 Hz, 4.3 Hz, 1H, H-20b), 2.28~2.41 (m, 4H, H-

16, H-2'b, H-2''b), 2.56 (m, 1H, H-12), 3.14~3.47 (m, 9H, H-25, H-4', H-2, 3''-OCH₃, 3'-OCH₃), 3.67~4.04 (m, 7H, H-3', H-17, H-3'', H-5'', H-5', H-13, H-6), 4.30 (br d, J = 5.9 Hz, 1H, H-5), 4.65~5.04 (m, 5H, H-27, H-1', H-15, H-4''), 5.42~5.45 (m, 3H, H-1'', H-3, H-19), 5.73~5.88 (m, 3H, H-10, H-11, H-9); ¹³C NMR (100 MHz, CDCl₃), δ: 173.7, 165.9, 139.7, 137.9, 137.8, 135.0, 133.1, 130.1, 129.7, 129.7, 128.4, 128.4, 124.8, 120.3, 118.3, 118.0, 98.5, 97.4, 94.8, 81.7, 81.0, 80.3, 79.2, 79.1, 76.8, 75.9, 75.9, 68.4, 68.4, 67.7, 67.3, 67.2, 66.7, 57.3, 56.7, 45.7, 41.1, 39.7, 37.0, 35.6, 35.2, 34.6, 34.2, 34.2, 27.8, 25.6,

20.3, 19.9, 18.4, 17.8, 17.5, 15.2, 10.0; HRESI-MS: $C_{53}H_{74}O_{15}$, 973.491 6[M+Na]⁺, 计算值 973.492 8.

8b: 4''-*O*-氯乙酰基天维菌素 B。收率 87%, 白色粉末; m.p. 125.8~129.5 °C; ¹H NMR (400 MHz, CDCl₃), δ: 0.81~0.89 (m, 4H, H-30, H-18a), 1.00 (t, *J* = 7.1 Hz, 3H, H-32), 1.17~1.42 (m, 12H, H-28, H-6', H-6'', H-24, H-31a, H-20a), 1.52~1.61 (m, 8H, H-29, H-22a, H-23, H-2''a, H-2'a), 1.65~1.81 (m, 3H, H-22b, H-31b, H-18b), 1.88 (br s, 3H, H-26), 2.00 (dd, *J* = 11.9, 4.1 Hz, 1H, H-20b), 2.24~2.38 (m, 4H, H-16, H-2'b, H-2''b), 2.54 (m, 1H, H-12), 3.11~3.45 (m, 9H, H-25, H-4', H-2, 3''-OCH₃, 3'-OCH₃), 3.61~3.67 (m, 3H, H-3', H-17, H-3''), 3.83~3.98 (m, 4H, H-5'', H-5', H-13, H-6), 4.10 (s, 2H, ClCH₂-), 4.30 (br d, *J* = 5.7 Hz, 1H, H-5), 4.64~4.81 (m, 4H, H-27, H-4'', H-1'), 5.01 (br d, *J* = 10.4 Hz, 1H, H-15), 5.41~5.48 (m, 3H, H-1'', H-3, H-19), 5.73~5.85 (m, 3H, H-10, H-11, H-9); ¹³C NMR (100 MHz, CDCl₃), δ: 173.8, 166.6, 139.7, 137.9, 137.9, 134.9, 124.8, 120.3, 118.3, 118.0, 98.3, 97.4, 94.7, 81.7, 80.9, 80.3, 79.2, 79.1, 78.1, 75.9, 75.4, 68.4, 68.4, 67.7, 67.3, 67.0, 66.1, 56.8, 56.6, 45.7, 41.1, 40.8, 39.7, 37.0, 35.6, 34.9, 34.6, 34.2, 34.2, 27.8, 25.6, 20.3, 20.0, 18.4, 17.8, 17.4, 15.2, 10.0; HRESI-MS: $C_{48}H_{71}ClO_{15}$, 945.436 6 [M+Na]⁺, 计算值 945.437 4.

8c: 4''-*O*-乙酰基天维菌素 B。收率 72%, 白色粉末; m.p. 136.9~140.7 °C; ¹H NMR (400 MHz, CDCl₃), δ: 0.81~0.90 (m, 4H, H-30, H-18a), 1.01 (t, *J* = 7.2 Hz, 3H, H-32), 1.14~1.43 (m, 12H, H-28, H-6', H-6'', H-24, H-31a, H-20a), 1.53~1.63 (m, 8H, H-29, H-22a, H-23, H-2''a, H-2'a), 1.66~1.81 (m, 3H, H-22b, H-31b, H-18b), 1.88 (br s, 3H, H-26), 2.00~2.05 (m, 1H, H-20b), 2.00~2.05 (m, 3H, CH₃CO-), 2.23~2.39 (m, 4H, H-16, H-2'b, H-2''b), 2.55 (m, 1H, H-12), 3.12~3.45 (m, 9H, H-25, H-4', H-2, 3''-OCH₃, 3'-OCH₃), 3.58~3.68 (m, 3H, H-3', H-17, H-3''), 3.83~4.00 (m, 4H, H-5'', H-5', H-13, H-6), 4.31 (br d, *J* = 5.9 Hz, 1H, H-5), 4.67~4.82 (m, 4H, H-27, H-1', H-4''), 5.00 (br d, *J* = 10.5 Hz, 1H, H-15), 5.42~5.48 (m, 3H, H-1'', H-3, H-19), 5.74~5.89 (m, 3H, H-10, H-11, H-9); ¹³C NMR (100 MHz, CDCl₃), δ: 173.8, 167.8, 139.7, 137.9, 137.9, 135.0, 124.8, 120.3, 118.3,

118.0, 98.3, 97.4, 94.7, 81.7, 80.6, 80.3, 79.2, 79.1, 75.9, 75.8, 75.7, 68.4, 68.4, 67.7, 67.3, 67.1, 66.5, 57.1, 56.6, 45.7, 41.1, 39.7, 37.0, 35.6, 34.6, 34.2, 34.2, 34.2, 27.8, 25.6, 21.8, 21.0, 19.9, 18.4, 17.8, 17.3, 15.2, 10.0; HRESI-MS: $C_{48}H_{72}O_{15}$, 911.474 3, [M+Na]⁺, 计算值 911.476 3.

8d: 4''-*O*-(4-氯-3-硝基)-苯甲酰基天维菌素 B。收率 85%, 白色粉末; m.p. 153.5~156.7 °C; ¹H NMR (400 MHz, CDCl₃), δ: 0.84~0.90 (m, 4H, H-30, H-18a), 1.01 (t, *J* = 7.0 Hz, 3H, H-32), 1.19~1.43 (m, 12H, H-28, H-6', H-6'', H-24, H-31a, H-20a), 1.53~1.63 (m, 8H, H-29, H-22a, H-23, H-2''a, H-2'a), 1.68~1.82 (m, 3H, H-22b, H-31b, H-18b), 1.89 (br s, 3H, H-26), 2.01 (dd, *J* = 12.0 Hz, 4.3 Hz, 1H, H-20b), 2.28~2.45 (m, 4H, H-16, H-2'b, H-2''b), 2.56 (m, 1H, H-12), 3.12~3.47 (m, 9H, H-25, H-4', H-2, 3''-OCH₃, 3'-OCH₃), 3.67~3.82 (m, 3H, H-3', H-17, H-3''), 3.88~4.05 (m, 4H, H-5'', H-5', H-13, H-6), 4.31 (br d, *J* = 5.8 Hz, 1H, H-5), 4.66~4.97 (m, 4H, H-27, H-1', H-4''), 5.03 (br d, *J* = 10.3 Hz, 1H, H-15), 5.42~5.49 (m, 3H, H-1'', H-3, H-19), 5.71~5.89 (m, 3H, H-10, H-11, H-9), 7.68~8.52 (m, 3H, aryl-H); ¹³C NMR (100 MHz, CDCl₃) δ: 173.8, 163.1, 147.9, 139.7, 137.9, 137.9, 135.0, 133.9, 132.2, 131.8, 130.0, 126.5, 124.8, 120.3, 118.3, 118.0, 98.6, 97.4, 94.7, 81.7, 81.3, 80.3, 79.2, 79.1, 78.0, 75.9, 75.6, 68.4, 68.4, 67.7, 67.3, 67.1, 66.3, 56.8, 56.6, 45.7, 41.1, 39.7, 37.0, 35.6, 35.0, 34.6, 34.2, 34.2, 27.8, 25.6, 20.4, 20.0, 18.5, 17.8, 17.5, 15.2, 10.0; HRESI-MS: $C_{53}H_{72}ClNO_{17}$, 1052.437 1[M+Na]⁺, 计算值 1052.438 1.

8e: 4''-*O*-丙烯酰基天维菌素 B。收率 82%, 白色粉末; m.p. 142.2~145.9 °C; ¹H NMR (400 MHz, CDCl₃), δ: 0.88~0.93 (m, 4H, H-30, H-18a), 1.04 (t, *J* = 7.1 Hz, 3H, H-32), 1.19~1.46 (m, 12H, H-28, H-6', H-6'', H-24, H-31a, H-20a), 1.56~1.65 (m, 8H, H-29, H-22a, H-23, H-2''a, H-2'a), 1.71~1.85 (m, 3H, H-22b, H-31b, H-18b), 1.92 (br s, 3H, H-26), 2.04 (dd, *J* = 11.8 Hz, 4.7 Hz, 1H, H-20b), 2.28~2.39 (m, 4H, H-16, H-2'b, H-2''b), 2.58 (m, 1H, H-12), 3.15~3.33 (m, 3H, H-25, H-4', H-2), 3.40~3.49 (m, 6H, 3''-OCH₃, 3'-OCH₃), 3.64~3.74 (m, 3H, H-3', H-17, H-3''), 3.88~4.01 (m, 4H, H-5'', H-5', H-13, H-6), 4.34

(br d, $J = 5.6$ Hz, 1H, H-5), 4.68~4.84 (m, 4H, H-27, H-1', H-4''), 5.00 (br d, $J = 10.2$ Hz, 1H, H-15), 5.45~5.52 (m, 3H, H-1'', H-3, H-19), 5.77~6.50 (m, 6H, H-10, H-11, H-9, CH₂=CHCO-); ¹³C NMR (100 MHz, CDCl₃), δ : 173.7, 165.4, 139.8, 137.9, 137.9, 134.9, 131.1, 128.3, 124.8, 120.3, 118.4, 118.0, 98.4, 97.4, 94.8, 81.7, 80.9, 80.3, 79.2, 79.1, 76.5, 75.9, 75.7, 68.4, 68.4, 67.7, 67.3, 67.2, 66.5, 57.0, 56.6, 45.7, 41.1, 39.8, 37.0, 35.6, 35.1, 34.7, 34.2, 34.1, 27.8, 25.6, 20.2, 19.9, 18.4, 17.7, 17.4, 15.2, 10.0; HRESI-MS: C₄₉H₇₂O₁₅, 923.476 6[M+Na]⁺, 计算值 923.477 3.

8f: 4''-O-乙酰氧基乙酰基天维菌素 B。收率 88%, 白色粉末; m.p. 118.8~121.6 °C; ¹H NMR (400 MHz, CDCl₃), δ : 0.84~0.90 (m, 4H, H-30, H-18a), 1.01 (t, $J = 7.0$ Hz, 3H, H-32), 1.17~1.44 (m, 12H, H-28, H-6', H-6'', H-24, H-31a, H-20a), 1.53~1.62 (m, 8H, H-29, H-22a, H-23, H-2''a, H-2'a), 1.66~1.82 (m, 3H, H-22b, H-31b, H-18b), 1.90 (br s, 3H, H-26), 2.01 (dd, $J = 11.8$ Hz, 4.1 Hz, 1H, H-20b), 2.19 (s, 3H, CH₃CO-), 2.28~2.37 (m, 4H, H-16, H-2'b, H-2''b), 2.55 (m, 1H, H-12), 3.12~3.45 (m, 9H, H-25, H-4', H-2, 3''-OCH₃, 3'-OCH₃), 3.62~3.68 (m, 3H, H-3', H-17, H-3''), 3.84~4.00 (m, 4H, H-5'', H-5', H-13, H-6), 4.32 (br d, $J = 5.7$ Hz, 1H, H-5), 4.60~4.82 (m, 6H, H-27, H-1', H-4'', -COCH₂CO-), 5.02 (br d, $J = 10.3$ Hz, 1H, H-15), 5.43~5.48 (m, 3H, H-1'', H-3, H-19), 5.70~5.88 (m, 3H, H-10, H-11, H-9); ¹³C NMR (100 MHz, CDCl₃) δ : 173.8, 170.3, 167.3, 139.7, 137.9, 137.9, 135.0, 124.8, 120.3, 118.3, 118.0, 98.3, 97.4, 94.8, 81.7, 80.7, 80.3, 79.2, 79.0, 77.3, 75.9, 75.4, 68.5, 68.4, 67.7, 67.3, 67.1, 66.2, 60.7, 56.9, 56.6, 45.7, 41.1, 39.7, 37.0, 35.6, 34.7, 34.2, 34.2, 29.7, 27.8, 25.6, 20.5, 20.3, 20.0, 18.4, 17.8, 17.4, 15.2, 10.0; HRESI-MS: C₅₀H₇₄O₁₇, 969.482 1[M+Na]⁺, 计算值 969.482 8.

8g: 4''-O-苯乙酰基天维菌素 B。收率 43%, 白色粉末; m.p. 136.8~139.9 °C; ¹H NMR (400 MHz, CDCl₃), δ : 0.80~0.89 (m, 4H, H-30, H-18a), 0.98~1.06 (m, 6H, H-32, H-6''), 1.18 (d, $J = 6.9$ Hz, 3H, H-28), 1.26~1.40 (m, 6H, H-6', H-24, H-31a, H-20a), 1.52~1.80 (m, 11H, H-29, H-22, H-23, H-2''a,

H-2'a, H-31b, H-18b), 1.89 (br s, 3H, H-26), 2.00 (dd, $J = 11.9$ Hz, 4.1 Hz, 1H, H-20b), 2.24~2.37 (m, 4H, H-16, H-2'b, H-2''b), 2.54 (m, 1H, H-12), 3.15~3.43 (m, 9H, H-25, H-4', H-2, 3''-OCH₃, 3'-OCH₃), 3.53~3.70 (m, 5H, H-3', H-17, H-3'', -CH₂CO-), 3.79~3.99 (m, 4H, H-5'', H-5', H-13, H-6), 4.31 (br d, $J = 5.8$ Hz, 1H, H-5), 4.65~4.81 (m, 4H, H-27, H-1', H-4''), 5.01 (br d, $J = 10.3$ Hz, 1H, H-15), 5.38~5.47 (m, 3H, H-1'', H-3, H-19), 5.73~5.88 (m, 3H, H-10, H-11, H-9), 7.27~7.33 (m, 5H, ph-H); ¹³C NMR (100 MHz, CDCl₃), δ : 173.8, 170.7, 139.8, 138.0, 137.9, 135.0, 134.0, 129.2, 129.2, 128.5, 128.5, 127.1, 124.8, 120.3, 118.3, 118.0, 98.4, 97.4, 94.8, 81.7, 80.8, 80.3, 79.3, 79.0, 76.7, 76.0, 75.7, 68.5, 68.4, 67.7, 67.3, 67.1, 66.4, 56.8, 56.6, 45.8, 41.7, 41.2, 39.8, 37.0, 35.6, 35.0, 34.7, 34.2, 34.2, 27.8, 25.6, 20.3, 20.0, 18.4, 17.8, 17.3, 15.2, 10.0; HRESI-MS: C₅₄H₇₆O₁₅, 987.507 9[M+Na]⁺, 计算值 987.508 5.

8h: 4''-O-对氟苯甲酰基天维菌素 B。收率 85%, 白色粉末; m.p. 121.2~123.6 °C; ¹H NMR (400 MHz, CDCl₃), δ : 0.83~0.90 (m, 4H, H-30, H-18a), 1.01 (t, $J = 7.0$ Hz, 3H, H-32), 1.19~1.42 (m, 12H, H-28, H-6', H-6'', H-24, H-31a, H-20a), 1.53~1.82 (m, 11H, H-29, H-22, H-23, H-2''a, H-2'a, H-31b, H-18b), 1.88 (br s, 3H, H-26), 2.02 (dd, $J = 12.0$ Hz, 4.3 Hz, 1H, H-20b), 2.28~2.42 (m, 4H, H-16, H-2'b, H-2''b), 2.55 (m, 1H, H-12), 3.12~3.47 (m, 9H, H-25, H-4', H-2, 3''-OCH₃, 3'-OCH₃), 3.66~3.80 (m, 3H, H-3', H-17, H-3''), 3.88~4.03 (m, 4H, H-5'', H-5', H-13, H-6), 4.31 (br d, $J = 5.8$ Hz, 1H, H-5), 4.65~4.95 (m, 4H, H-27, H-1', H-4''), 5.03 (br d, $J = 10.8$ Hz, 1H, H-15), 5.42~5.48 (m, 3H, H-1'', H-3, H-19), 5.75~5.89 (m, 3H, H-10, H-11, H-9), 7.13~8.10 (m, 4H, aryl-H); ¹³C NMR (100 MHz, CDCl₃), δ : 173.8, 167.1, 163.9, 139.7, 137.9, 137.9, 135.0, 132.3, 132.3, 126.3, 124.8, 120.3, 118.3, 118.0, 115.7, 115.4, 98.5, 97.4, 94.8, 81.8, 81.0, 80.3, 79.2, 79.1, 76.3, 75.9, 75.8, 68.4, 68.4, 67.7, 67.3, 67.1, 66.6, 57.2, 56.6, 45.7, 41.1, 39.7, 37.0, 35.6, 35.2, 34.6, 34.2, 34.2, 27.8, 25.6, 20.3, 19.9, 18.4, 17.8, 17.5, 15.2, 10.0; HRESI-MS: C₅₃H₇₃FO₁₅, 991.483 2[M+Na]⁺, 计算值 991.483 6.

8i: 4''-O-三氯乙酰基天维菌素 B。收率 87%,

白色粉末; m.p. 136.8~139.6 °C; ¹H NMR (400 MHz, CDCl₃), δ: 0.84~0.90 (m, 4H, H-30, H-18a), 1.01 (t, *J* = 6.9 Hz, 3H, H-32), 1.18~1.43 (m, 12H, H-28, H-6', H-6'', H-24, H-31a, H-20a), 1.53~1.61 (m, 8H, H-29, H-22a, H-23, H-2''a, H-2'a), 1.68~1.81 (m, 3H, H-22b, H-31b, H-18b), 1.89 (br s, 3H, H-26), 2.03 (dd, *J* = 11.9 Hz, 4.3 Hz, 1H, H-20b), 2.28~2.44 (m, 4H, H-16, H-2'b, H-2''b), 2.55 (m, 1H, H-12), 3.12~3.46 (m, 9H, H-25, H-4', H-2, 3''-OCH₃, 3'-OCH₃), 3.65~3.76 (m, 3H, H-3', H-17, H-3''), 3.85~4.03 (m, 4H, H-5'', H-5', H-13, H-6), 4.30 (br d, *J* = 5.7 Hz, 1H, H-5), 4.65~4.82 (m, 4H, H-27, H-4'', H-1'), 5.01 (br d, *J* = 10.1 Hz, 1H, H-15), 5.42~5.49 (m, 3H, H-1'', H-3, H-19), 5.74~5.88 (m, 3H, H-10, H-11, H-9); ¹³C NMR (100 MHz, CDCl₃), δ: 173.8, 161.2, 139.7, 137.9, 137.9, 135.0, 124.8, 120.3, 118.3, 118.0, 98.5, 97.4, 94.7, 90.0, 81.7, 81.5, 81.4, 80.3, 79.2, 79.1, 75.9, 75.5, 68.4, 68.4, 67.7, 67.3, 67.0, 65.8, 57.3, 56.6, 45.7, 41.1, 39.7, 37.0, 35.6, 35.2, 34.6, 34.2, 34.2, 27.8, 25.6, 20.3, 20.0, 18.4, 17.8, 17.2, 15.2, 10.0; HRESI-MS: C₄₈H₆₉Cl₃O₁₅, 1 013.368 0 [M+Na]⁺, 计算值 1 013.369 4.

8j: 4'-*O*-二氯乙酰基天维菌素 B。收率 87%, 白色粉末; m.p. 139.8~143.5 °C; ¹H NMR (400 MHz, CDCl₃), δ: 0.83~0.89 (m, 4H, H-30, H-18a), 1.00 (t, *J* = 7.0 Hz, 3H, H-32), 1.19~1.43 (m, 12H, H-28, H-6', H-6'', H-24, H-31a, H-20a), 1.52~1.62 (m, 8H, H-29, H-22a, H-23, H-2''a, H-2'a), 1.65~1.80 (m, 3H, H-22b, H-31b, H-18b), 1.88 (br s, 3H, H-26), 2.00 (dd, *J* = 12.0 Hz, 4.3 Hz, 1H, H-20b), 2.27~2.41 (m, 4H, H-16, H-2'b, H-2''b), 2.54 (m, 1H, H-12), 3.11~3.45 (m, 9H, H-25, H-4', H-2, 3''-OCH₃, 3'-OCH₃), 3.61~3.73 (m, 3H, H-3', H-17, H-3''), 3.84~3.98 (m, 4H, H-5'', H-5', H-13, H-6), 4.30 (br d, *J* = 5.6 Hz, 1H, H-5), 4.65~4.81 (m, 4H, H-27, H-4'', H-1'), 5.01 (br d, *J* = 10.3 Hz, 1H, H-15), 5.41~5.47 (m, 3H, H-1'', H-3, H-19), 5.73~5.88 (m, 3H, H-10, H-11, H-9), 6.00 (s, 1H, Cl₂CHCO-); ¹³C NMR (100 MHz, CDCl₃), δ: 173.8, 163.8, 139.8, 137.9, 137.9, 135.0, 124.8, 120.3, 118.3, 118.0, 98.5, 97.4, 94.7, 81.7, 81.2, 80.3, 79.5, 79.2, 79.1, 75.9, 75.4, 68.4, 68.4, 67.7, 67.3, 67.0, 66.0, 64.4, 57.2, 56.6, 45.7, 41.1,

39.8, 37.0, 35.6, 35.1, 34.6, 34.2, 34.2, 27.8, 25.6, 20.3, 20.0, 18.4, 17.8, 17.2, 15.2, 10.0; HRESI-MS: C₄₈H₇₀Cl₂O₁₅, 979.397 3 [M+Na]⁺, 计算值 979.398 4.

1.2.3.2 4'-*O*-酰基天维菌素 B 单糖苷衍生物 (**9a-9h**) 合成通法 合成方法同 1.2.3.1 节。

9a: 4'-*O*-苯甲酰基天维菌素 B 单糖苷。收率 82%, 白色粉末; m.p. 131.2~134.6 °C; ¹H NMR (400 MHz, CDCl₃), δ: 0.82~0.89 (m, 4H, H-30, H-18a), 1.00 (t, *J* = 7.1 Hz, 3H, H-32), 1.18~1.41 (m, 9H, H-28, H-6', H-24, H-31a, H-20a), 1.48~1.81 (m, 10H, H-29, H-22, H-23, H-2'a, H-31b, H-18b), 1.87 (br s, 3H, H-26), 2.00 (dd, *J* = 11.9 Hz, 4.1 Hz, 1H, H-20b), 2.27~2.38 (m, 3H, H-16, H-2'b), 2.56 (m, 1H, H-12), 3.10~3.29 (m, 2H, H-25, H-2), 3.40 (s, 3H, 3'-OCH₃), 3.68~3.85 (m, 2H, H-3', H-17), 3.96~4.10 (m, 3H, H-13, H-6, H-5'), 4.29 (br d, *J* = 5.8 Hz, 1H, H-5), 4.64~4.73 (m, 2H, H-27), 4.89~4.97 (m, 2H, H-4', H-1'), 5.04 (br d, *J* = 10.4 Hz, 1H, H-15), 5.41~5.46 (m, 2H, H-3, H-19), 5.71~5.90 (m, 3H, H-10, H-11, H-9), 7.46~8.09 (m, 5H, ph-H); ¹³C NMR (100 MHz, CDCl₃), δ: 173.7, 165.9, 139.9, 137.9, 137.7, 134.9, 133.1, 130.0, 129.8, 129.8, 128.4, 128.4, 124.9, 120.3, 118.4, 118.0, 97.4, 94.9, 81.9, 80.3, 79.1, 76.9, 76.0, 75.9, 68.4, 68.4, 67.7, 67.3, 66.6, 57.6, 45.7, 41.1, 39.7, 37.0, 35.6, 35.2, 34.2, 34.2, 27.8, 25.7, 20.3, 20.0, 17.8, 17.5, 15.2, 10.0; HRESI-MS: C₄₆H₆₂O₁₂, 829.411 5 [M+Na]⁺, 计算值 829.413 3.

9b: 4'-*O*-氯乙酰基天维菌素 B 单糖苷。收率 84%, 白色粉末; m.p. 144.4~147.5 °C; ¹H NMR (400 MHz, CDCl₃), δ: 0.81~0.90 (m, 4H, H-30, H-18a), 1.02 (t, *J* = 7.2 Hz, 3H, H-32), 1.17~1.43 (m, 9H, H-28, H-6', H-24, H-31a, H-20a), 1.53~1.59 (m, 7H, H-29, H-22a, H-23, H-2'a), 1.68~1.81 (m, 3H, H-22b, H-31b, H-18b), 1.89 (br s, 3H, H-26), 2.01 (dd, *J* = 12.1 Hz, 4.4 Hz, 1H, H-20b), 2.25~2.39 (m, 3H, H-16, H-2'b), 2.55 (m, 1H, H-12), 3.12~3.30 (m, 2H, H-25, H-2), 3.43 (s, 3H, 3'-OCH₃), 3.65~3.75 (m, 2H, H-3', H-17), 3.97~4.02 (m, 3H, H-5', H-13, H-6), 4.12 (s, 2H, ClCH₂-), 4.31 (br d, *J* = 5.8 Hz, 1H, H-5), 4.65~4.88 (m, 4H, H-27, H-4', H-1'), 5.02 (br d, *J* = 10.2 Hz, 1H, H-15), 5.42~5.47 (m, 2H, H-3, H-19), 5.74~5.89 (m, 3H, H-10, H-11, H-9); ¹³C NMR (100 MHz,

CDCl₃) δ : 173.8, 166.8, 139.9, 137.9, 137.6, 134.8, 124.9, 120.3, 118.4, 118.0, 97.4, 94.7, 81.8, 80.3, 79.1, 78.0, 75.9, 75.6, 68.5, 68.4, 67.7, 67.3, 66.1, 57.1, 45.7, 41.1, 40.9, 39.7, 37.0, 35.6, 34.8, 34.2, 34.2, 27.8, 25.6, 20.3, 20.0, 17.8, 17.4, 15.2, 10.0; HRESI-MS: C₄₁H₅₉ClO₁₂, 801.359 1[M+Na]⁺, 计算值 801.359 9.

9c: 4'-*O*-乙酰基天维菌素 B 单糖苷。收率 80%, 白色粉末; m.p. 146.5~149.3 °C; ¹H NMR (400 MHz, CDCl₃), δ : 0.81~0.90 (m, 4H, H-30, H-18a), 1.02 (t, J = 7.1 Hz, 3H, H-32), 1.14~1.43 (m, 9H, H-28, H-6', H-24, H-31a, H-20a), 1.52~1.62 (m, 7H, H-29, H-22a, H-23, H-2'a), 1.70~1.81 (m, 3H, H-22b, H-31b, H-18b), 1.89 (br s, 3H, H-26), 2.01 (dd, J = 12.0 Hz, 4.4 Hz, 1H, H-20b), 2.13 (s, 3H, CH₃CO-), 2.28~2.35 (m, 3H, H-16, H-2'b), 2.54 (m, 1H, H-12), 3.11~3.29 (m, 2H, H-25, H-2), 3.44 (s, 3H, 3'-OCH₃), 3.65~3.71 (m, 2H, H-3', H-17), 3.91~3.99 (m, 3H, H-5', H-13, H-6), 4.30 (br d, J = 5.8 Hz, 1H, H-5), 4.65~4.86 (m, 4H, H-27, H-4', H-1'), 5.02 (br d, J = 10.4 Hz, 1H, H-15), 5.42~5.47 (m, 2H, H-3, H-19), 5.70~5.89 (m, 3H, H-10, H-11, H-9); ¹³C NMR (100 MHz, CDCl₃), δ : 173.8, 170.4, 139.8, 137.9, 137.8, 134.8, 124.8, 120.3, 118.4, 118.3, 97.4, 94.7, 81.7, 80.3, 79.1, 76.2, 75.9, 75.8, 68.5, 68.4, 67.7, 67.3, 66.4, 57.2, 45.7, 41.1, 39.7, 37.0, 35.6, 34.9, 34.2, 34.2, 27.8, 25.6, 21.1, 20.2, 20.0, 17.8, 17.4, 15.2, 10.0; HRESI-MS: C₄₁H₆₀O₁₂, 767.397 5 [M+Na]⁺, 计算值 767.397 7.

9d: 4'-*O*-(4-氯-3-硝基)-苯甲酰基天维菌素 B 单糖苷。收率 82%, 白色粉末; m.p. 139.4~142.6 °C; ¹H NMR (400 MHz, CDCl₃), δ : 0.85~0.92 (m, 4H, H-30, H-18a), 1.02 (t, J = 7.1 Hz, 3H, H-32), 1.20~1.44 (m, 9H, H-28, H-6', H-24, H-31a, H-20a), 1.52~1.83 (m, 10H, H-29, H-22, H-23, H-2'a, H-31b, H-18b), 1.90 (br s, 3H, H-26), 2.02 (dd, J = 11.9 Hz, 4.2 Hz, 1H, H-20b), 2.27~2.41 (m, 3H, H-16, H-2'b), 2.59 (m, 1H, H-12), 3.13~3.31 (m, 2H, H-25, H-2), 3.41 (s, 3H, 3'-OCH₃), 3.67~3.88 (m, 2H, H-3', H-17), 4.00~4.14 (m, 3H, H-13, H-6, H-5'), 4.32 (br d, J = 6.0 Hz, 1H, H-5), 4.67~5.00 (m, 4H, H-27, H-4', H-1'), 5.05 (br d, J = 10.3 Hz, 1H, H-15), 5.43~5.49 (m,

2H, H-3, H-19), 5.77~5.91 (m, 3H, H-10, H-11, H-9), 7.70~8.54 (m, 3H, aryl-H); ¹³C NMR (100 MHz, CDCl₃), δ : 173.8, 163.2, 148.1, 139.9, 137.9, 137.6, 134.8, 133.8, 132.2, 131.8, 129.9, 126.6, 125.0, 120.3, 118.5, 118.0, 97.4, 94.8, 82.1, 80.3, 79.1, 78.0, 75.9, 75.8, 68.5, 68.4, 67.7, 67.3, 66.3, 57.1, 45.7, 41.1, 39.7, 37.0, 35.6, 35.0, 34.2, 34.1, 27.8, 25.6, 20.4, 20.0, 17.8, 17.5, 15.2, 10.0; HRESI-MS: C₄₆H₆₀ClNO₁₄, 908.358 5[M+Na]⁺, 计算值 908.359 5.

9e: 4'-*O*-丙烯酰基天维菌素 B 单糖苷。收率 80%, 白色粉末; m.p. 135.4~138.3 °C; ¹H NMR (400 MHz, CDCl₃), δ : 0.83~0.89 (m, 4H, H-30, H-18a), 1.01 (t, J = 7.0 Hz, 3H, H-32), 1.15~1.19 (m, 6H, H-28, H-6'), 1.37~1.42 (m, 3H, H-24, H-31a, H-20a), 1.52~1.55 (m, 6H, H-29, H-22a, H-23), 1.70~1.81 (m, 4H, H-2'a, H-22b, H-31b, H-18b), 1.88 (br s, 3H, H-26), 2.00 (dd, J = 12.0 Hz, 4.3 Hz, 1H, H-20b), 2.24~2.35 (m, 3H, H-16, H-2'b), 2.55 (m, 1H, H-12), 3.11~3.29 (m, 2H, H-25, H-2), 3.42 (s, 3H, 3'-OCH₃), 3.69~3.71 (m, 2H, H-3', H-17), 3.97~4.01 (m, 3H, H-5', H-13, H-6), 4.31 (br d, J = 5.7 Hz, 1H, H-5), 4.65~4.87 (m, 4H, H-27, H-4', H-1'), 5.02 (br d, J = 10.2 Hz, 1H, H-15), 5.41~5.44 (m, 2H, H-3, H-19), 5.70~6.50 (m, 6H, H-10, H-11, H-9, CH₂=CHCO-); ¹³C NMR (100 MHz, CDCl₃), δ : 173.8, 165.6, 139.8, 137.9, 137.8, 134.8, 131.4, 128.2, 124.9, 120.3, 118.4, 118.0, 97.4, 94.8, 81.7, 80.3, 79.1, 77.4, 75.9, 75.8, 68.5, 68.4, 67.7, 67.3, 66.5, 57.4, 45.7, 41.1, 39.7, 37.0, 35.6, 35.0, 34.2, 34.2, 27.8, 25.7, 20.3, 20.0, 17.8, 17.4, 15.2, 10.0; HRESI-MS: C₄₃H₆₂O₁₄, 779.397 9[M+Na]⁺, 计算值 779.398 7.

9f: 4'-*O*-乙酰氧基乙酰基天维菌素 B 单糖苷。收率 84%, 白色粉末; m.p. 139.4~142.6 °C; ¹H NMR (400 MHz, CDCl₃), δ : 0.83~0.89 (m, 4H, H-30, H-18a), 1.00 (t, J = 7.0 Hz, 3H, H-32), 1.15~1.41 (m, 9H, H-28, H-6', H-24, H-31a, H-20a), 1.52~1.58 (m, 7H, H-29, H-22a, H-23, H-2'a), 1.68~1.80 (m, 3H, H-22b, H-31b, H-18b), 1.88 (br s, 3H, H-26), 2.00 (dd, J = 12.0 Hz, 4.3 Hz, 1H, H-20b), 2.17 (s, 3H, CH₃CO-), 2.24~2.35 (m, 3H, H-16, H-2'b), 2.54 (m, 1H, H-12), 3.10~3.28 (m, 2H, H-25, H-2), 3.42 (s, 3H, 3'-OCH₃), 3.65~3.71 (m, 2H, H-3', H-17), 3.91~3.99 (m, 3H, H-

5', H-13, H-6), 4.29 (br d, $J = 5.4$ Hz, 1H, H-5), 4.60~4.85 (m, 6H, H-27, H-4', H-1', -COCH₂CO-), 5.00 (br d, $J = 10.2$ Hz, 1H, H-15), 5.41~5.47 (m, 2H, H-3, H-19), 5.73~5.89 (m, 3H, H-10, H-11, H-9); ¹³C NMR (100 MHz, CDCl₃), δ : 173.8, 170.3, 167.3, 139.9, 138.0, 137.7, 134.8, 124.9, 120.3, 118.4, 118.0, 97.4, 94.6, 81.7, 80.3, 79.1, 77.3, 75.9, 75.5, 68.5, 68.4, 67.7, 67.3, 66.2, 60.7, 57.2, 45.7, 41.1, 39.7, 37.0, 35.6, 34.9, 34.2, 27.8, 25.6, 20.4, 20.2, 20.0, 17.8, 17.4, 15.2, 10.0; HRESI-MS: C₄₃H₆₂O₁₄, 825.403 6[M+Na]⁺, 计算值 825.404 2.

9g: 4'-*O*-苯乙酰基天维菌素 B 单糖苷。收率 75%, 白色粉末; m.p. 131.4~134.2 °C; ¹H NMR (400 MHz, CDCl₃), δ : 0.81~0.88 (m, 4H, H-30, H-18a), 0.97~1.04 (m, 6H, H-32, H-6'), 1.15 (d, $J = 6.8$ Hz, 3H, H-28), 1.34~1.40 (m, 3H, H-24, H-31a, H-20a), 1.52~1.58 (m, 6H, H-29, H-22a, H-23), 1.63~1.79 (m, 4H, H-2'a, H-22b, H-31b, H-18b), 1.88 (br s, 3H, H-26), 2.00 (dd, $J = 12.0$ Hz, 4.1Hz, 1H, H-20b), 2.22~2.33 (m, 3H, H-16, H-2'b), 2.53 (m, 1H, H-12), 3.12 (t, $J = 9.0$ Hz, 1H, H-25), 3.27 (s, 4H, 3'-OCH₃, H-2), 3.58~3.67 (m, 4H, H-3', H-17, -CH₂CO-), 3.88~3.96 (m, 3H, H-5', H-13, H-6), 4.29 (br d, $J = 5.6$ Hz, 1H, H-5), 4.63~4.83 (m, 4H, H-27, H-4', H-1'), 5.00 (br d, $J = 10.2$ Hz, 1H, H-15), 5.40~5.44 (m, 2H, H-3, H-19), 5.72~5.85 (m, 3H, H-10, H-11, H-9), 7.25~7.32 (m, 5H, ph-H); ¹³C NMR (100 MHz, CDCl₃), δ : 173.7, 170.8, 139.8, 137.8, 137.7, 134.8, 133.9, 129.2, 129.2, 128.5, 128.5, 127.1, 124.9, 120.3, 118.4, 118.0, 97.4, 94.7, 81.7, 80.3, 79.2, 76.5, 75.9, 75.8, 68.4, 68.4, 67.7, 67.3, 66.4, 57.1, 45.7, 41.7, 41.1, 39.7, 37.0, 35.6, 34.9, 34.2, 27.8, 25.6, 20.2, 19.9, 17.8, 17.3, 15.2, 10.0; HRESI-MS: C₄₇H₆₄O₁₂, 843.427 3[M+Na]⁺, 计算值 843.429 0.

9h: 4'-*O*-对氟苯甲酰基天维菌素 B 单糖苷。收率 84%, 白色粉末; m.p. 142.5~144.9 °C; ¹H NMR (400MHz, CDCl₃), δ : 0.82~0.90 (m, 4H, H-30, H-18a), 1.00 (t, $J = 7.2$ Hz, 3H, H-32), 1.17~1.21 (m, 6H, H-28, H-6'), 1.33~1.41 (m, 3H, H-24, H-31a, H-20a), 1.48~1.58 (m, 6H, H-29, H-22a, H-23), 1.66~1.81 (m, 4H, H-2'a, H-22b, H-31b, H-18b), 1.87 (br s, 3H, H-26), 2.01 (dd, $J = 12.0$ Hz, 4.2Hz, 1H, H-

20b), 2.24~2.37 (m, 3H, H-16, H-2'b), 2.56 (m, 1H, H-12), 3.13~3.29 (m, 2H, H-25, H-2), 3.39 (s, 3H, 3'-OCH₃), 3.66~3.84 (m, 2H, H-3', H-17), 3.95~4.11 (m, 3H, H-13, H-6, H-5'), 4.29 (br d, $J = 5.9$ Hz, 1H, H-5), 4.64~4.73 (m, 2H, H-27), 4.89~4.95 (m, 2H, H-4', H-1'), 5.04 (br d, $J = 10.4$ Hz, 1H, H-15), 5.41~5.45 (m, 2H, H-3, H-19), 5.75~5.89 (m, 3H, H-10, H-11, H-9), 7.13~8.11 (m, 4H, aryl-H); ¹³C NMR (100 MHz, CDCl₃), δ : 173.7, 164.9, 164.6, 139.9, 137.8, 137.7, 134.9, 132.4, 132.3, 126.2, 124.9, 120.3, 118.5, 118.0, 115.7, 115.5, 97.4, 94.9, 81.9, 80.3, 79.2, 77.0, 76.0, 75.9, 68.4, 68.4, 67.7, 67.3, 66.6, 57.4, 45.7, 41.1, 39.7, 37.0, 35.6, 35.1, 34.2, 34.1, 27.8, 25.6, 20.3, 19.9, 17.8, 17.5, 15.2, 10.0; HRESI-MS: C₄₆H₆₁FO₁₂, 847.401 8 [M+Na]⁺, 计算值 847.403 9.

1.2.3.3 13-*O*-酰基天维菌素 B 苷元衍生物 (10a~10e) 合成通法 合成方法同 1.2.3.1 节。

10a: 13-*O*-苯甲酰基天维菌素 B 苷元。收率 74%, 淡黄色粉末; m.p. 149.7~153.8 °C; ¹H NMR (400 MHz, CDCl₃), δ : 0.80 (d, $J = 6.3$ Hz, 3H, H-30), 0.87~0.97 (m, 4H, H-18a, H-32), 1.14 (d, $J = 6.8$ Hz, 3H, H-28), 1.28~1.42 (m, 3H, H-24, H-31a, H-20a), 1.48~1.83 (m, 9H, H-29, H-22, H-23, H-31b, H-18b), 1.91 (br s, 3H, H-26), 2.03 (dd, $J = 11.9$ Hz, 4.0Hz, 1H, H-20b), 2.26~2.31 (m, 2H, H-16), 2.80 (m, 1H, H-12), 3.05 (m, 1H, H-25), 3.32 (s, 1H, H-2), 3.59 (m, 1H, H-17), 4.01 (d, $J = 6.1$ Hz, 1H, H-6), 4.33 (br d, $J = 6.1$ Hz, 1H, H-5), 4.69~4.78 (m, 2H, H-27), 5.14 (br d, $J = 10.2$ Hz, 1H, H-15), 5.44~5.48 (m, 3H, H-13, H-3, H-19), 5.86~5.94 (m, 3H, H-10, H-11, H-9), 7.54~8.16 (m, 5H, ph-H); ¹³C NMR (100 MHz, CDCl₃), δ : 173.6, 165.5, 140.7, 137.9, 136.7, 134.6, 133.3, 130.0, 129.7, 129.7, 128.6, 128.6, 125.5, 120.0, 118.1, 117.8, 97.4, 80.3, 80.3, 79.2, 75.8, 68.5, 68.4, 67.7, 67.2, 45.7, 41.2, 39.4, 36.8, 35.6, 34.2, 34.0, 27.7, 25.6, 19.9, 18.9, 17.7, 14.7, 9.8; HRESI-MS: 661.337 3, C₃₉H₅₀O₉[M-H]⁻, 计算值 661.338 5.

10b: 13-*O*-氯乙酰基天维菌素 B 苷元。收率 79%, 淡黄色粉末; m.p. 144.4~147.5 °C; ¹H NMR (400 MHz, CDCl₃), δ : 0.83~0.91 (m, 4H, H-30, H-18a), 1.01 (t, $J = 7.2$ Hz, 3H, H-32), 1.09 (d, $J = 6.8$ Hz, 3H, H-28), 1.35~1.41 (m, 3H, H-24, H-31a, H-20a),

1.50~1.76 (m, 9H, H-29, H-22, H-23, H-31b, H-18b), 1.89 (br s, 3H, H-26), 2.02 (dd, $J = 12.0$ Hz, 4.4Hz, 1H, H-20b), 2.22~2.31 (m, 2H, H-16), 2.69 (m, 1H, H-12), 3.10 (m, 1H, H-25), 3.28 (s, 1H, H-2), 3.64 (m, 1H, H-17), 3.98 (d, $J = 6.1$ Hz, 1H, H-6), 4.18 (s, 2H, ClCH₂-), 4.31 (br d, $J = 6.1$ Hz, 1H, H-5), 4.65~4.74 (m, 2H, H-27), 5.07 (br d, $J = 7.7$ Hz, 1H, H-15), 5.23(br s, 1H, H-13), 5.38~5.45 (m, 2H, H-3, H-19), 5.65~5.88 (m, 3H, H-10, H-11, H-9); ¹³C NMR (100 MHz, CDCl₃), δ : 173.5, 166.4, 140.9, 137.9, 136.0, 133.8, 125.6, 119.9, 118.1, 118.0, 97.4, 80.5, 80.3, 79.1, 76.0, 68.4, 68.4, 67.7, 67.1, 45.6, 41.1, 40.8, 39.2, 36.9, 35.6, 34.2, 34.1, 27.8, 25.7, 19.9, 18.7, 17.8, 14.6, 10.0; HRESI-MS: C₃₄H₄₇ClO₉, 633.282 0[M-H]⁻, 计算值 633.283 2.

10c: 13-*O*-乙酰基天维菌素 B 苷元。收率 62%, 淡黄色粉末; m.p. 134.2~137.0 °C; ¹H NMR (400 MHz, CDCl₃), δ : 0.84~0.90 (m, 4H, H-30, H-18a), 1.01~1.08 (m, 6H, H-32, H-28), 1.35~1.40 (m, 3H, H-24, H-31a, H-20a), 1.52~1.76 (m, 9H, H-29, H-22, H-23, H-31b, H-18b), 1.89 (br s, 3H, H-26), 2.00 (dd, $J = 12.0$ Hz, 4.4Hz, 1H, H-20b), 2.21~2.32 (m, 5H, H-16, CH₃CO-), 2.67 (m, 1H, H-12), 3.11 (m, 1H, H-25), 3.27 (s, 1H, H-2), 3.64 (m, 1H, H-17), 3.97 (d, $J = 6.1$ Hz, 1H, H-6), 4.30 (br d, $J = 6.1$ Hz, 1H, H-5), 4.64~4.73 (m, 2H, H-27), 5.08 (br d, $J = 10.4$ Hz, 1H, H-15), 5.20(br s, 1H, H-13), 5.38~5.45 (m, 2H, H-3, H-19), 5.61~5.83 (m, 3H, H-10, H-11, H-9); ¹³C NMR (100 MHz, CDCl₃), δ : 173.6, 166.2, 140.7, 137.9, 136.4, 133.9, 125.4, 120.0, 118.2, 118.0, 97.4, 80.3, 79.9, 79.1, 76.0, 68.4, 68.4, 67.7, 67.1, 45.6, 41.2, 39.1, 36.9, 35.6, 34.2, 34.2, 30.4, 27.8, 25.7, 19.9, 18.7, 17.8, 14.6, 10.1; HRESI-MS: C₃₄H₄₈O₉, 599.320 3[M-H]⁻, 计算值 599.322 6.

10d: 13-*O*-(4-氯-3-硝基)-苯甲酰基天维菌素 B 苷元。收率 77%, 淡黄色粉末; m.p. 139.4~142.6 °C; ¹H NMR (400 MHz, CDCl₃), δ : 0.79 (d, $J = 6.3$ Hz, 3H, H-30), 0.86~0.96 (m, 4H, H-18a, H-32), 1.13 (d, $J = 6.8$ Hz, 3H, H-28), 1.27~1.41 (m, 3H, H-24, H-31a, H-20a), 1.47~1.80 (m, 9H, H-29, H-22, H-23, H-31b, H-18b), 1.89 (br s, 3H, H-26), 2.02 (dd, $J = 12.0$ Hz, 4.4 Hz, 1H, H-20b), 2.26~2.31 (m, 2H, H-16), 2.81

(m, 1H, H-12), 3.04 (m, 1H, H-25), 3.30 (s, 1H, H-2), 3.59 (m, 1H, H-17), 4.00 (d, $J = 6.1$ Hz, 1H, H-6), 4.32 (br d, $J = 5.8$ Hz, 1H, H-5), 4.67~4.77 (m, 2H, H-27), 5.03 (br d, $J = 10.2$ Hz, 1H, H-15), 5.42~5.46 (m, 3H, H-13, H-3, H-19), 5.75~5.95 (m, 3H, H-10, H-11, H-9), 7.73~8.55 (m, 3H, aryl-H); ¹³C NMR (100 MHz, CDCl₃), δ : 173.5, 162.8, 148.3, 141.3, 137.9, 135.6, 134.2, 133.4, 132.4, 131.9, 129.9, 126.6, 126.0, 119.8, 118.0, 118.0, 97.4, 80.7, 80.3, 79.1, 75.8, 68.4, 68.4, 67.7, 67.0, 45.6, 41.2, 39.3, 36.9, 35.6, 34.2, 34.0, 27.7, 25.6, 20.0, 18.9, 17.7, 14.7, 9.8; HRESI-MS: C₃₉H₄₈ClNO₁₁, 740.283 8[M-H]⁻, 计算值 740.284 8.

10e: 13-*O*-丙烯酰基天维菌素 B 苷元。收率 67%, 淡黄色粉末; m.p. 144.4~147.5 °C; ¹H NMR (400 MHz, CDCl₃), δ : 0.81~0.91 (m, 4H, H-30, H-18a), 0.99 (t, $J = 7.1$ Hz, 3H, H-32), 1.06 (d, $J = 6.7$ Hz, 3H, H-28), 1.35~1.40 (m, 3H, H-24, H-31a, H-20a), 1.48~1.78 (m, 9H, H-29, H-22, H-23, H-31b, H-18b), 1.88 (br s, 3H, H-26), 2.00 (dd, $J = 12.0$ Hz, 4.2 Hz, 1H, H-20b), 2.21~2.29 (m, 2H, H-16), 2.69 (m, 1H, H-12), 3.08 (m, 1H, H-25), 3.28 (s, 1H, H-2), 3.61 (m, 1H, H-17), 3.98 (d, $J = 6.0$ Hz, 1H, H-6), 4.30 (br d, $J = 5.7$ Hz, 1H, H-5), 4.65~4.74 (m, 2H, H-27), 5.03 (br d, $J = 5.6$ Hz, 1H, H-15), 5.22(br s, 1H, H-13), 5.41~5.45 (m, 2H, H-3, H-19), 5.69~6.51 (m, 6H, H-10, H-11, H-9, CH₂ = CHCO-); ¹³C NMR (100 MHz, CDCl₃), δ : 173.6, 165.3, 140.6, 137.9, 136.8, 134.4, 131.3, 128.2, 125.3, 120.1, 118.0, 117.7, 97.4, 80.3, 79.1, 78.8, 75.9, 68.4, 68.4, 67.7, 67.2, 45.7, 41.2, 39.2, 36.9, 35.6, 34.2, 34.1, 27.8, 25.7, 19.9, 18.7, 17.7, 14.6, 10.0; HRESI-MS: C₃₅H₄₈O₉, 611.321 1 [M-H]⁻, 计算值 611.321 .

1.3 杀虫、杀螨活性测定

供试试虫来源于生物农药高效制备技术国家地方联合工程实验室, 在人工气候室条件下 [(26 ± 1) °C, RH(70 ± 5)%, H/D14/10h] 饲养。小菜蛾 *Plutella xylostella*: 接种于萝卜苗上培养。朱砂叶螨 *Tetranychus cinnabarinus*, 接种于蚕豆苗上培养, 以雌成螨作为试虫。松材线虫 *Bursaphelenchus xylophilus*, 以灰葡萄孢饲养。以 3~4 龄幼虫作为线虫源。

1.3.1 对小菜蛾的杀虫活性测定 采用药膜法^[7,18]。将天维菌素 B 酰化衍生物用丙酮溶解, 稀释成系列质量浓度为 5、10、25、50、100 mg/L 的药液, 备用。选择室内饲养、生理状态一致的 2~3 龄幼虫。对照用天维菌素 B 处理, 每浓度为 1 处理, 每处理重复 3 次。统计 48 h 后幼虫死亡情况。

1.3.2 对朱砂叶螨室内杀螨活性测定 采用叶碟浸渍法^[7,19]。分别将天维菌素 B 酰化衍生物用丙酮溶解, 稀释成系列质量浓度 0.001、0.005、0.01、0.05、0.1 mg/L 的药液, 备用。选择室内饲养、生理状态一致的雌成螨虫接种于直径 2 cm 蚕豆叶碟, 每叶碟 30 头, 定殖 2 h 后确定每叶碟上螨的数量不低于 20 头。对照用天维菌素 B 处理, 每个浓度为 1 处理, 每处理重复 3 次。将叶碟从低浓度到高浓度依次浸药 10 s。待叶片上的药剂晾干, 置于人工气候室培养, 24 h 后于体视显微镜下统计朱砂叶螨死亡情况。

1.3.3 对松材线虫室内活性测定 采用浸渍法^[7,20]测定化合物对松材线虫室内杀虫活性。将其配制成 2500 条/mL 左右的线虫液备用。分别将天维菌素 B 酰化衍生物用丙酮溶解, 稀释成质量浓度为 20.0、10.0、5.0、2.5、1.0、0.5 mg/L 的溶液。各取 10 μ L 供试药液和 90 μ L 松材线虫悬浮液于 96 孔培养板中。以含天维菌素 B 的乳油为对照。每浓度为 1 处理, 每处理重复 3 次。24 h 后在镜检查松材线虫死亡情况。

1.3.4 数据分析 用 Abbott 公式计算死亡率并加以校正。

校正死亡率 = (处理组死亡率 - 对照组死亡率) / (1 - 对照组死亡率) \times 100%, 并用软件 SPSS19.0 计算 LC₅₀ 值。

2 结果与分析

2.1 目标化合物的合成

中间体化合物单糖、无糖天维菌素采用催化水解法制备, 控制反应时间和酸的浓度能精准控制目标化合物的生成。单糖天维菌素的合成条件选择酸浓度为 3%, 反应时间 15 h 为宜; 无糖天维菌素选择酸浓度为 5%, 反应时间 20 h 更佳。另外, 在 C-5 位羟基上保护反应中, 选用 TBDMS-Cl 作为保护基团时底物反应充分, 收率较好^[21]。当 GF₂₅₄ 硅胶板监测中间体 7a~7j 的 R_f 值在 0.65~

0.75 之间、控制反应时间 0.5~2 h 时可减少副产物的生成。

在天维菌素 B 4'' 位的酰基化反应中, 与苯乙酰氯 (g) 的反应时间最久, 约 2 h, 且总收率仅为 43%, 其余酰氯均在 1 h 内完成反应, 且总收率 72% 以上; 单糖天维菌素 B 除了与酰氯 i、j 反应后易被 *p*-TSA 水解外, 其余均成功反应, 且反应很快, 几乎滴加的同时即完成反应, 无需保温, 反应总收率 75% 以上; 由于 13 位羟基相较于 4'' 位、4' 位的位阻较大, 活性较低, 因此能与无糖天维菌素 B 成功反应的酰氯仅为 a~e, 均在 2 h 内完成, 反应的总收率 62% 上。由此可见, 羟基反应活性为单糖天维菌素 B 优于天维菌素 B 和无糖天维菌素 B。

对天维菌素 B、天维菌素 B 单糖苷和天维菌素 B 苷元的 C-4''、C-4' 及 C-4 羟基进行酰化反应后, 氢谱变化最明显的是 H-4'' 的化学位移值, 由 3.17 移动至 4.6~5.0 之间, 天维菌素 B 单糖苷 H-4'' 的化学位移值由 3.25 移动至 4.6~5.0 之间, 天维菌素 B 苷元 H-13 的化学位移值由 3.95 移动至 4.2~5.5 之间, 而碳谱中变化最明显则是在 160~170 之间多出一个相应羰基信号, 同时出现反应基团的核磁信号。

2.2 杀虫、杀螨活性

由目标化合物对小菜蛾、朱砂叶螨和松材线的生物活性测定结果 (表 1) 可见: 天维菌素 B C-4'' 衍生物对 3 种测试靶标的活性明显优于天维菌素 B C-4' 和 C-13 衍生物。由化合物的 LC₅₀ 值可以看出: 脱去 1 个糖基和脱去 2 个糖基, 衍生物的活性分别下降 5~10 倍和 50 倍以上。与天维菌素 B 相比, 天维菌素 B C-4'' 酰化衍生物 8a~8c、8e、8f~8i 对小菜蛾活性更优, 其中 8e 和 8h 活性最好, 其 LC₅₀ 值分别为 9.2 和 12.7 mg/L; 对朱砂叶螨的活性结果表明, 仅 8b、8c 和 8e 的杀螨活性优于天维菌素 B, 化合物 8d 和 8g~8j 的活性与天维菌素 B 相当; 对松材线虫的活性数据可以看出, 仅化合物 8b 和 8e 的活性优于天维菌素 B (LC₅₀=0.73 mg/L), 其 LC₅₀ 值分别为 0.69 和 0.42 mg/L; 其他化合物活性均弱于母体化合物。通过筛选, 化合物 8e 对 3 种试虫均具有较好的毒杀活性。

3 结论

表 1 天维菌素 B 衍生物的杀虫杀螨活性

Table 1 Insecticidal and acaricidal activities of tenvermectin B derivatives against *Plutella xylostella*, *Tetranychus cinnabarinus* and *Bursaphelenchus xylophilus*

化合物 Compd.	LC ₅₀ 值(95%置信区间) LC ₅₀ value (95 CL)/(mg/L)		
	小菜蛾 <i>P. xylostella</i>	朱砂叶螨 <i>T. cinnabarinus</i>	松材线虫 <i>B. xylophilus</i>
8a	42.3(25.4~76.3)	0.014 3(0.010 1~0.020 3)	1.73(1.43~2.10)
8b	36.9(17.9~56.2)	0.001 9(0.001 3~0.002 7)	0.69(0.52~0.92)
8c	27.4(18.1~41.4)	0.002 1(0.001 5~0.002 8)	0.86(0.64~1.16)
8d	95.9(48.5~122.5)	0.002 9(0.001 6~0.004 2)	6.83(4.63~10.1)
8e	9.2(6.1~14.8)	0.002 7(0.001 9~0.003 7)	0.42(0.31~0.57)
8f	32.5(12.9~81.8)	0.015 5(0.008 8~0.027 3)	1.85(1.55~2.21)
8g	143.2(94.7~194.9)	0.003 9(0.002 6~0.006 1)	2.90(2.29~3.66)
8h	12.7(4.4~26.4)	0.003 1(0.002 0~0.004 9)	1.68(1.41~2.00)
8i	43.4(21.3~68.1)	0.003 4(0.002 1~0.005 3)	0.91(0.74~1.12)
8j	76.2(54.4~102.2)	0.004 2(0.002 8~0.006 3)	1.09(0.91~1.31)
9a	523(441~625)	0.934(0.765~1.123)	9.15(7.88~11.45)
9b	529(413~701)	0.106(0.089 7~0.143)	3.25(2.92~4.07)
9c	552(400~661)	0.112(0.098~0.156)	5.80(5.01~7.89)
9d	606(512~691)	0.223(0.189~0.246)	16.8(12.81~21.34)
9e	487(367~628)	0.122(0.101~0.149)	2.79(1.99~4.01)
9f	554(490~719)	0.712(0.668~0.826)	10.5(8.46~14.25)
9g	822(682~930)	0.237(0.202~0.311)	13.5(10.62~16.11)
9h	588(413~689)	0.155(0.104~0.249)	7.68(5.99~9.29)
10a	>1 000	4.58	6.34
10b	>1 000	0.68	21.3
10c	>1 000	1.50	9.74
10d	>1 000	1.03	15.1
10e	>1 000	3.12	51.3
天维菌素 B 苷元 tenvermectin B aglycone	>1 000	1.27	11.3
天维菌素 B 单糖苷 tenvermectin B monosaccharide	570(498~651)	0.142(0.112~1.189)	6.34(5.87~6.99)
天维菌素 B tenvermectin B	50.1(41.1~61.1)	0.002 8(0.002 1~0.003 7)	0.73(0.58~0.91)

以天维菌素 B 结构为母体, 设计并合成了 3 个系列共 23 个天维菌素酰化衍生物, 其结构均经过 ¹H NMR、¹³C NMR 和 HRMS 确证。杀虫、杀螨活性测定结果表明, 化合物 **8e** 对 3 种试虫均具有较好的毒杀活性。初步的结构-活性关系分析结果表明, 在所合成的天维菌素 B 酰化衍生物中, 侧链 2 个糖基对于保持化合物的活性具有非常重要的作用。当脱去糖基时其活性大大降低, 这与先前研究结果^[14-15]相似。在化合物 **8a~8j** 中, 不同取代基链的长短及体积对活性影响并没有呈现明显规律。当化合物 C-4'' 位被含不同取代基的苯环取代时, 甲基、乙基等给电子基团取代基的活性明显高于吸电子基团 (卤素、硝基) 取代的衍生物, 但氟原子基团 (**8h**) 的引入却极大的提

高了对小菜蛾的活性, 而对其他 2 种试虫活性没有明显变化。对不同种类的试虫活性测定结果表明, 天维菌素 B C-4'' 衍生物的活性差异较大。而 C13-OH 构型发生变化后并引入相关活性官能团的乐平霉素 (lepimectin)^[14] 却保持该类化合物的活性且毒性更低, 这就进一步说明衍生物杀虫、杀螨活性的差异应该与多种影响因素有关, 如取代基的体积、电子分布和给电子特性等。本研究结果表明, 通过在天维菌素 B 4''-位引入酰基活性结构单元在防治小菜蛾方面具有很大潜质。

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