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5-依维菌素 B_{1a}酯的合成和生物活性

廖联安[a] 李正名*,[b] 方红云[a] 赵 卫光[b] 范志金[b] 刘桂龙[b]
([a] 厦门大学化学系 福建 361005)
([b] 南开大学元素有机化学研究所 元素有机化学重点实验室 天津 300071)

摘要 依维菌素 B_{1a}与羧酸在 DMAP/DCC 体系中直接酯化, 得到 10 个 5-Ⅳ B_{1a}酯衍生物, 产率 66% ~ 82%; 它们的化学结构得到 IR, ^{1}H NMR, ^{13}C NMR 和 MS 谱的确证. 它们具有良好的杀虫、杀螨活性.

关键词 酯化, 5-依维菌素 B_{1a}酯, 生物活性, DMAP/DCC

Synthesis and Bioactivity of 5-Ivermectin B_{1a} Esters

LIAO, Lian-An[a] LI, Zheng-Ming*,[b] FANG, Hong-Yun[a]
ZHAO, Wei-Guang[b] FAN, Zhi-Jin[b] LIU, Gui-Long[b]
([a]*Department of Chemistry, Xiamen University, Xiamen 361005*)
([b]*Institute of Elemento-Organic Chemistry, Nankai University, Tianjin 300071*)

Abstract Ten 5-Ivermectin B_{1a} ester derivatives were prepared from Ivermectin B_{1a} and carboxylic acids in the systems of DCC/DMAP. Their chemical structures were determined by IR, ^{1}H NMR, ^{13}C NMR and MS spectra. The preliminary results of bioassay showed that **L-1 ~ L-10** have good insecticidal activities.

Keywords esterification, 5-Ivermectin B_{1a}, bioactivity, DMAP/DCC

依维菌素是阿维菌素[1~3]的二氢化物, 属于十六元环内酯衍生物. 依维菌素的主要成分为 22, 23-二氢 AV B_{1a}, 根据测试, B_{1a}杀虫活性最高, 其他异构体杀虫活性较低而且毒性高. 依维菌素对家畜的肠内寄生虫具有极其有效的驱虫活性, 并具有作用机制独特、有效剂量低、安全性高等特点, 广泛用于畜牧业和宠物保健; 在医药上依维菌素用于治疗人类由于螨虫或线虫引起的疾病, 极为有效[4].

为进一步提高其活性和稳定性、扩展(改变)其活性谱、降低毒性, 许多化学家对它的结构进行了各种改造, 合成了许多衍生物, 并从中推出了几个比母体化合物活性更好的化合物, 如 4″-C 羟基的改造产物 Emamectin[5] 和 Eprinomectin[6], 其活性比母体化合物提高了 1 ~ 2 个数量级, 正在商品化进程中. 本文依据生物活性基团拼接原理, 在母体分子中引入生物活性片段、杂环和杂原子, 设计合成了 10 个 5-依维菌素 B_{1a}酯, 并初筛了它们的杀虫、杀螨活性.

1 结果与讨论

在早期文献[7,8]中 5-依维菌素 B_{1a}酯的制备方法是用大过量的酸酐或酰氯与依维菌素反应, 产率仅 30% ~ 50%, 而且选择性不理想, 通常得到 5-酯和 4″-、5-双酯. DMAP 对酯(酰)化反应是优良的催化剂, 与脱水剂 DCC 合用, 羧酸可以在很温和的条件下直接与醇反应生成高产率的酯[9]. 我们将这一体系应用于依维菌素 B_{1a}酯的合成, 发现用 1.1 当量的羧酸可以高效、高选择性地进行反应, 产率良好. 所

* E-mail: zml@tjlink.tisti.ac.cn
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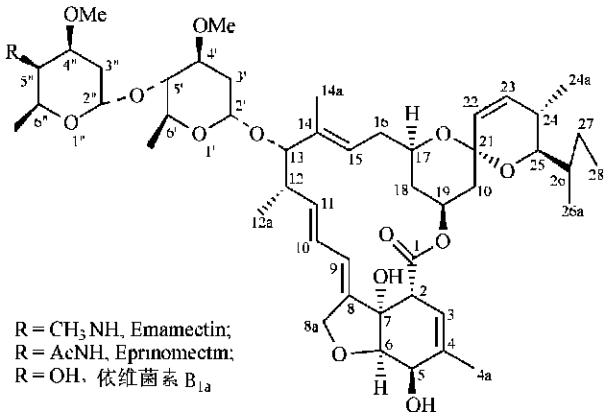

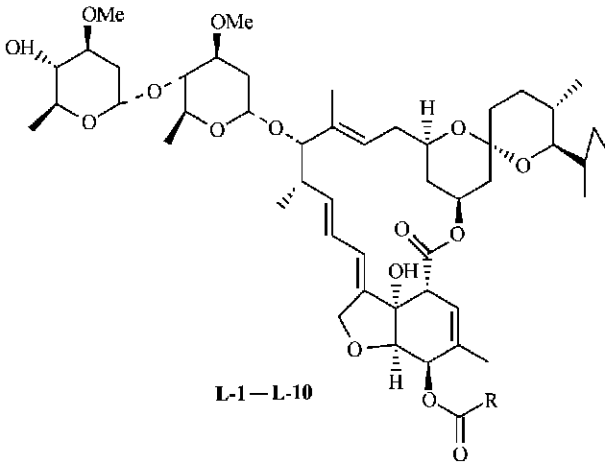

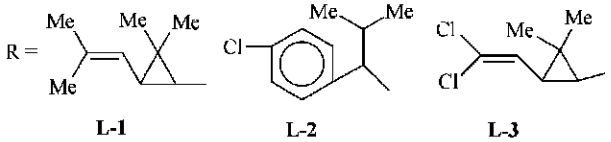

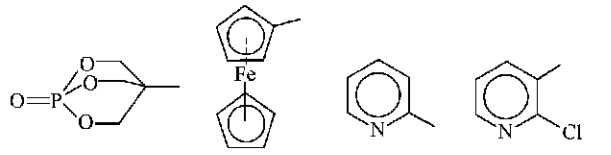

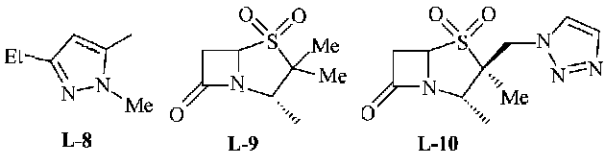

制备的 10 个 5-依维菌素 B_{1a}酯均系新化合物. 化合物的化学结构得到 IR, ^{1}H NMR, ^{13}C NMR 和 MS 谱的确证.

由于依维菌素系列化合物对酸碱均不稳定, 所以整个合成和后处理过程中, 必须尽可能避免长时间与酸碱接触或处于高温状态, 否则这些化合物都会发生异构化、分子内脱水和开环降解等副反应. 因此, 反应物羧酸必须先与 DCC 反应, 生成物混合酸酐可以溶解在二氯甲烷中, 然后再加入依维菌素原料和催化剂 DMAP, 这样反应就可以顺利进行, 反应中伴有大约 3%~5%的4″-位和 5-位双酯生成. 大过量(1∶1.5 或更高)的羧酸会导致4″-位和5-位双酯的大量生成而影响分离. 反应在室温下进行, 当提高反应温度至 50 ℃以上, 会使 C(3)═C(4)双键移位成 C(2)═C(3)双键和 7-位羟基的脱水.

由于依维菌素系列化合物大部分稳定性差, 我们采用大气压化学电离(APCI)和快原子轰击(FAB)来进行它们的质谱实验.

2　杀虫杀螨活性

2.1　对棉蚜杀虫活性的初筛试验

棉蚜(*Aphis gossypii* Glover)采自北京东北旺肖家河菜地的白瓜叶上. 取干净新鲜的瓜叶一小片, 用小号毛笔将大小、体色一致的蚜虫挑选 30 头于其上, 将叶片连试虫一起浸入药液中 2 s 后取出, 立即用吸水纸将蚜虫周围多余的药液吸净, 将叶片放入 50 mL 的塑料杯中, 杯口用纱布以橡皮筋套紧以防蚜虫逃逸. 将试虫放入(27±1) ℃相对湿度 85%的恢复室中, 16 h 后检查结果. 死亡标准为, 以小号毛笔轻触动虫体, 试虫不动且无任何反应者视为死亡, 以死虫数占总虫数的百分数为死亡率[10]. 同时设清水对照, 以清水对照按 Abbott 公式计算校正死亡率. 每药剂设 0.50 mg/L 和 2.00 mg/L 两个浓度, 各浓度重复 2~3 次. 由于在商品依维菌素中含有的少量 B_{1b}组分与 B_{1a}组分的杀虫活性相近, 纯化后的依维菌素与商品药剂杀虫活性一致, 因此我们选用商品依维菌素为对照药剂(表 1).

2.2　对红蜘蛛杀螨活力的初筛试验

参照 FAO (1980)的方法改进[11]. 棉叶螨的品种为截形叶螨 (*Tetranychus truncatus* Ehara), 采自河北省农科院植保所, 为相对敏感种群. 经室内饲养纯化后使用. 试螨饲养在光照培养箱中, 光照 14 h/d, 温度(27±1) ℃, 相对湿度 60%~75%. 饲料为新鲜的蚕 (*Phaseolus vulgaris* L.)豆苗.

将双面胶带剪成 2 cm 左右的长度, 贴在载玻片的一端, 用小号毛笔将 3~4 日龄的雌成螨背部粘在胶带上, 注意螨足和触须及口器不能被粘着, 每载玻片粘两行, 每行 10~15 头. 将其放入直径 10 cm 的培养皿中, 用棉球吸水保湿. 4 h 后在双目解剖镜下用解剖针挑除死亡个体或者生活力明显低下及受伤的个体. 将药剂配成一定浓度的水溶液后, 将试螨在药液中浸泡 5 s, 取出后用吸水纸轻轻吸去试螨周围

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表 1 5-依维菌素 B_{1a}酯对棉蚜虫的杀虫活性

Table 1 Bioactivity of 5-Ⅳ B_{1a} esters against *Aphis gossypii* Glover

Compd.	校正死亡率（%）		Compd.	校正死亡率（%）	
	0.50 mg/L	2.00 mg/L		0.50 mg/L	2.00 mg/L
CK[a]	10.12		Ⅳ[b]	26.47	47.78
L-1	8.73	56.72	**L-6**	15.93	36.41
L-2	25.01	42.19	**L-7**	32.81	49.61
L-3	21.95	30.20	**L-8**	52.59	72.15
L-4	35.09	42.23	**L-9**	61.60	62.87
L-5	6.35	6.55	**L-10**	19.94	38.09

[a] CK 为空白对照, 26次平均值; [b] Ⅳ 为依维菌素药剂对照, 13 次平均值.

表 2 依维菌素 B_{1a}酯对红蜘蛛的杀螨活性

Table 2 Bioactivity of 5-ⅣB_{1a} esters against *Tetranychus truncatus* Ehara[a]

Compd.	CK	Ⅳ	L-1	L-2	L-3	L-4	L-5	L-6	L-7	L-8	L-9	L-10
死亡率（%）	0	52.4	83.3	5.7	47.6	73.5	0	76.0	61.4	70.0	58.8	2.8

[a] 10 次实验的平均值.

多余的药液, 避免损伤螨体. 将试螨放入(27±1) ℃相对湿度 85%的恢复室中, 24 h 后在双目解剖镜下检查结果. 死亡标准为, 以小号毛笔轻触动螨体, 试螨的触须、螨足和口器无任何反应(不动)者视为死亡, 以死螨数占总螨数的百分数为死亡率. 同时设清水为对照, 以清水对照按 Abbott 公式计算校正死亡率. 药剂浓度设为 1.00 mg/L, 各浓度重复 2 次(表 2).

Mrozik 等[7] 曾经对阿维菌素 5-位羟基进行了酯化研究, 结果发现 5-位酯化产物的生物活性明显下降. 然而从上述两表可以看出, 不同 5-位酯化产物对活性有不同的影响. 特别是化合物 **L-1** 和 **L-8** 对棉蚜和棉叶螨都具有较好的杀虫活性, 在相同剂量下比商品依维菌素的杀虫活性提高了 0.3 到 1.3 倍.

3 实验部分

3.1 仪器和试剂

所用的试剂为化学纯或分析纯, 溶剂经过重蒸后使用. 山东齐鲁制药厂提供了依维菌素[$w(B_1)$=98.1%, $w(B_{1a})$=94.2%, $w(B_{1b})$=3.9%] 样品.

X-4 型数字显示显微熔点测定仪, 温度计未校正. Alltech 426 液相色谱仪. Perkin Elmer Polarimeter 341 自动旋光仪(589 nm, $CHCl_3$). Shimadzu IR-435 红外光谱仪, KBr 压片. Bruker ACP-200 核磁共振仪、JEOL AL-300 核磁共振仪和 Varian UNITY-plus 400 磁共振仪 ($CDCl_3$, TMS 内标). Fisons ZAB-HS 质谱仪(FAB) 和 Finnigan MAT LCQ 质谱仪(APCI).

3.2 依维菌素 B_{1a}的分离和纯化

从依维菌素商品中分离出各个组分, 常用的方法是采用制备性液相色谱进行分离; 但只能够得到很少量的样品, 远远不能够满足合成上的需要. 我们经过实验摸索, 发现采用减压柱层析方法可以简便、大量地分离依维菌素商品中的 B_{1a}和 B_{1b}组分, 回收率达到92%, 高于文献[8] 的 75%, 操作极为简便, 并且层析柱可以重复使用. 分离方法如下:

依维菌素[$w(B_1)$=98.1%, $w(B_{1a})$=94.2%, $w(B_{1b})$=3.9%] 商品 3.00 g 溶解在少量的二氯甲烷中, 加入 1.0 g 硅胶, 减压旋干; 取出放在一根装有 20 g 硅胶的层析柱上, 减压柱层析, 用乙酸乙酯(EA)—石油醚(PE, 60~90 ℃)进行梯度淋洗, 先用 1∶2 EA-PE 淋洗, 洗脱出 AVB_{2a}和 AVB_{2b}; 再用 1∶1 EA-PE 淋洗, 得白色固体粉末 IVB_{1a} 2.60 g, 收率 87%, m.p. 155~157 ℃ (154.5~157 ℃[7]); ^{1}H NMR δ: 5.87 (d, J=10.1 Hz, 1H, 9-H), 5.74 (m, 2H, 10-H & 11-H), 5.34~5.43 (m, 3H, 3-H, 1″-H & 19-H), 4.98 (d, J=6.8 Hz, 1H, 15-H), 4.78 (s, 1H, 1′-H), 4.69 (s, 2H, 8a-H_2), 4.30 (d, J=6.1 Hz, 1H, 5-H), 3.98 (d, J=6.5 Hz, 1H, 6-H), 3.95 (d, J=3.6 Hz, 2H, 17-H & 13-H), 3.60~3.80 (m, 4H, 5″-H, 5′-H, 3″-H & 3′-H), 3.40 (s, 3H, OCH_3), 3.39 (s, 3H, OCH_3), 3.10~3.24 (m, 4H, 4″-H, 4′-H, 2-H & 25-H), 2.60~2.80 (br, 3H, 3×OH), 2.53 (m, 1H, 12-H), 2.20~2.35 (m, 5H, 16-H_2, 24-H, 2′-

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H_2), 1.78～2.03 (m, 5H, 4-Me &18-H_2), 1.28～1.68 (m, 14H, 14-Me, 20-H_2, 26-H, 27-H_2, 2″-H_2, 22-H_2, 23H_2), 1.26 (d, J＝6.5 Hz, 3H, 5″-Me), 1.21～1.24 (d, J＝6.5 Hz, 3H, 5′-Me), 1.15 (d, J＝7.0 Hz, 3H, 12-Me), 0.90 (t, J＝7.0 Hz, 3H, 28-Me), 0.80～0.84 (d, J＝6.8 Hz, 3H, 26-Me), 0.76 (d, J＝7.2 Hz, 3H, 24-Me); ^{13}C NMR δ: 173.7 (1-C), 139.5 (8-C), 137.9 (11-C), 137.8 (4-C), 134.9 (14-C), 124.6 (10-C), 120.3 (9-C), 118.2 (3-C), 118.0 (15-C), 98.4 (1″-C), 97.4 (21-C), 94.7 (1′-C), 81.7 (13-C), 80.3 (4′-C), 79.3 (7-C), 79.1 (6-C), 78.1 (3′-C), 77.4 (3″-C), 77.0 (25-C), 76.6 (4″-C), 75.9 (5″-C), 68.6 (17-C), 68.3 (8a-C), 68.1 (5-C), 67.6 (5′-C), 67.1 (19-C), 56.4 (OCH_3), 56.3 (OCH_3), 45.6 (2-C), 41.1 (20-C), 39.6 (12-C), 36.8 (16-C), 35.9 (26-C), 35.4 (18-C), 34.2 (2″-C), 34.1 (2′-C), 34.0 (24-C), 31.1 (22-C), 28.0 (23-C), 27.2 (27-C), 20.2 (12a-C), 19.9 (4a-C), 18.3 (6″-C), 17.6 (6′-C), 17.4 (24a-C), 15.1 (14a-C), 12.4 (26a-C), 12.0 (28-C); IR (KBr) ν: 3443, 2966, 1733, 1457 1381, 1160, 1050, 987 cm^{-1}; MS (FAB) m/z (%): 891 (M^+＋Li, 100), 874 (M^+), 566 (M^+－Ole－Ole－H_2O).

3.3　5-依维菌素 B_{1a}酯的通用合成方法

在50 mL锥型瓶中, 加入TAZOBACTAM酸132 mg (0.44 mmol), N, N'-二环己基碳二亚胺(DCC) 91 mg (0.44 mmol)、4-二甲胺基吡啶(DMAP) 10 mg和25 mL二氯甲烷, 电磁搅拌溶解, 20 min后, 加入依维菌素B_{1a} 350 mg (0.40 mmol), 室温下搅拌反应6 h; 过滤除去生成的N, N'-二环己基脲(DCU), 滤液用3×10 mL水洗, 无水硫酸钠干燥, 旋转蒸发至干, 得淡黄色固体. 减压柱层析, 用EA-PE进行梯度淋洗, 得到366 mg淡黄色固体, m.p. 138～140 ℃, $[\alpha]_D^{25}$＋49.9 (c 1.06, $CHCl_3$), 波谱数据证明其化学结构为5-TZ-Ⅳ B_{1a}(**L-10**).

按同样方法合成了**L-1**至**L-9**, 其理化数据和波谱数据如下:

L-1, ^{1}H NMR δ: 5.82～5.84 (d, J＝9.6 Hz, 1H, 9-H), 5.72～5.75 (m, 2H, 10-H &11-H), 5.50～5.54 (d, J＝7.3 Hz, 1H, 3-H), 5.30～5.42 (m, 3H, Me_2C＝C**H**, 1″-H &19-H), 4.98～5.02 (d, 1H, J＝6.8 Hz, 15-H), 4.87～4.89 (d, J＝3.5 Hz, 1H, 1′-H), 4.78 (d, J＝2.6 Hz, 1H, 8a-H), 4.65～4.69 (m, 1H, 5-H), 4.56～4.58 (d, J＝3.5 Hz, 1H, 8a-H), 4.13 (br, 2H, 2×OH), 3.84～4.04 (m, 3H, 6-H, 17-H &13-H), 3.62～3.69 (m, 4H, 5″-H, 5′-H, 3″-H &3′-H), 3.34～3.43 (m, 2H, 25-H &2-H), 3.18～3.22 (m, 2H, 4′-H &4″-H), 2.52 (m, 1H, 12-H), 2.16～2.32 (m, 7H, 16-H_2, 24-H, 环丙烷片段的2个H &2′-H_2), 2.02～2.08 (m, 2H, 18-H_2), 1.93 (s, 9H, 4-Me &＝CMe_2), 1.57～1.82 (m, 14H, 20-H_2, 14-Me, 26-H, 27-H_2, 2″-H_2, 22-H_2 &23-H_2), 1.12～1.40 (m, 15H, 5′-Me, 5″-Me, 12-Me &环丙烷片段的2个Me), 0.79～0.98 (m, 9H, 28-Me, 26-Me &24-Me); IR (KBr) ν: 3386, 2915, 1725, 1689, 1645, 1559, 1445, 1218, 1050, 996 cm^{-1}; MS (APCI) m/z (%): 1024.5 (M^+, 16; 计算值, 1024.6123), 1047 (M^+＋Na, 8), 1006 (M^+－H_2O, 13).

L-2, ^{1}H NMR δ: 7.265～7.313 (m, 4H, 4-Cl-C_6H_4), 5.793～5.817 (m, 1H, 9-H), 5.655～5.712 (m, 2H, 10-H &11-H), 5.541 (s, 1H, 3-H), 5.486 (d, J＝4.0 Hz, 1H, 1″-H), 5.352 (m, 1H, 19-H), 4.988 (d, J＝7.0 Hz, 1H, 15-H), 4.763 (s, 1H, 1′-H), 4.607～4.653 (m, 2H, 8a-H_2), 4.415～4.445 (dd, J＝9.6 Hz, 3.5 Hz, 1H, 5-H), 4.124 (brs, 2H, 2×OH), 3.941～3.961 (m, 1H, 6-H), 3.708～3.821 (s, 1H, 13-H), 3.119～3.591 (m, 8H, 17-H, 2×OCH_3 &4″-H), 2.920 (d, J＝7.3 Hz, 1H, Ar-CH), 2.513 (m, 1H, 12-H), 2.238～2.369 (m, 6H, 16-H_2, 24-H, 2′-H_2 &Me_2C**H**), 2.014 (d, J＝6.5 Hz, 2H, 18-H_2), 1.620～1.745 (m, 18H, 4-Me, 14-Me, 20-H_2, 26-H, 27-H_2, 2″-H_2, 22-H_2 &23-H_2), 1.030～1.502 (m, 15H, 5′-Me, 5″-Me, 12-Me &CMe_2), 0.652～0.919 (m, 9H, 28-Me, 26-Me &24-Me); ^{13}C NMR δ: 173.646 (1-C), 154.039 (New, CO_2R), 139.761 (8-C), 138.010 (11-C), 137.895 (4-C), 135.249 (14-C), 133.215, 130.605, 130.118, 128.780, 128.711, 128.543 (6×Ar-C), 125.010 (10-C), 121.385 (9-C), 120.452 (3-C), 118.739 (15-C), 98.703 (1″-C), 97.732 (21-C), 95.163 (1′-C), 82.208 (13-C), 80.809 (7-C), 80.732 (6-C), 79.440 (3′-C), 78.326 (3″-C), 70.600 (25-C), 69.040 (4″-C), 67.480 (4′-C), 67.396 (17-C), 66.616 (8a-C), 60.154 (5-C), 59.833 (5′-C), 59.703 (5″-C), 58.624 (19-C), 56.835 (OMe), 56.705 (OMe), 50.534 (Me_2-C), 46.037 (2-C), 41.510 (20-C), 39.988 (12-C), 37.143 (16-C), 36.012 (Ar-C), 35.736 (26-C), 35.308 (18-C), 33.465 (2′-C), 33.090 (2″-C),

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32.907 (24-C), 31.454 (23-C), 31.079 (22-C), 26.307 (27-C), 25.642 (New Me), 24.977 (New Me), 21.826 (12a-C), 20.442 (4a-C), 18.599 (6″-C), 17.643 (6′-C), 17.574 (24a-C), 15.356 (14a-C), 12.596 (26a-C), 12.305 (28-C); IR (KBr) ν: 3395, 2945, 1732 (br), 1628, 1510, 1447, 1113, 1043, 981 cm^{-1}; MS (APCI) m/z (%): 1069.8 (M^+, 10; 计算值, 1069.7798), 1093 (M^++Na, 18), 1051 (M^+-H_2O, 43).

L-3, ^{1}H NMR δ: 6.26 (m, 1H, $Cl_2C=CH$), 5.83 (m, 1H, 9-H), 5.71 (m, 2H, 10-H & 11-H), 5.28~5.60 (m, 3H, 3-H, 1″-H, 19-H), 4.97 (d, J=6.7 Hz, 1H, 15-H), 4.76 (d, J=3.5 Hz, 1H, 1′-H), 4.58~4.69 (m, 2H, 8a-H_2), 4.28 (d, J=6.1 Hz, 1H, 5-H), 3.60~3.98 (m, 3H, 13-H, 6-H & 17-H), 3.73 (brs, 2H, 2×OH), 3.42 (s, 3H, OMe), 3.38 (s, 3H, OMe), 3.36~3.53 (m, 4H, 5″-H, 5′-H, 7H, 3″-H & 3′-H), 3.10~3.26 (m, 4H, 4″-H, 4′-H, 2-H & 25-H), 2.52 (m, 1H, 12-H), 2.23~2.35 (m, 16-H, 24-H, 2′-H & 环丙烷片段的两个H), 1.78~1.96 (m, 5H, 4-Me & 18-H_2), 1.30~1.68 (m, 14H, 14-Me, 20-H_2, 26-H, 27-H_2, 2″-H_2, 22-H_2 & 23-H_2), 1.13~1.28 (m, 15H, 5″-Me, 5′-Me, 12-Me & 环丙烷片段的两个Me), 0.81~0.90 (m, 9H, 28-Me, 26-Me & 24-Me); IR (KBr) ν: 3408, 2916, 1690, 1647, 1527, 1446, 1245, 1047, 993 cm^{-1}; MS (APCI) m/z (%): 1066.3 (M^+, 13; 计算值, 1066.1838), 1089 (M^++Na, 8), 1048 (M^+-H_2O, 26).

L-4, ^{1}H NMR δ: 6.03~6.10 (d, 1H, J=8.7 Hz, 9-H), 5.70~5.73 (m, 2H, 10-H & 11-H), 5.52 (m, 1H, 3-H), 5.34~5.41 (m, 2H, 1″-H & 19-H), 4.98 (d, J=7.0 Hz, 1H, 15-H), 4.81~4.86 (d, J=8.7 Hz, 6H, PO(OCH_2)$_3$C), 4.70~4.78 (m, 3H, 1′-H & 8a-H_2), 4.26~4.32 (d, J=6.1 Hz, 1H, 5-H), 4.07 (brs, 2H, 2×OH), 3.86~3.99 (m, 4H, 13-H, 6-H, 17-H & 5″-H), 3.62~3.71 (m, 3H, 5′-H, 3″-H & 3′-H), 3.40 (s, 3H, O-Me), 3.39 (s, 3H, O-Me), 3.10~3.18 (m, 4H, 4′-H, 4″-H, 2-H & 25-H), 2.52 (m, 1H, 12-H), 2.23 (m, 5H, 16-H_2, 24-H & 2′-H_2), 1.87~2.03 (m, 5H, 4-Me & 18-H_2), 1.53~1.74 (m, 14H, 20-H_2, 26-H, 27-H_2, 14-Me, 2″-H_2, 22-H_2 & 23-H_2), 1.12~1.40 (m, 9H, 5′-Me, 5″-Me & 12-Me), 0.79~0.98 (m, 9H, 28-Me, 26-Me & 24-Me); IR (KBr) ν: 3413, 2926, 1715, 1583, 1368, 1115, 1050, 981 cm^{-1}; MS (APCI) m/z (%): 1051.3 (M^+, 43; 计算值, 1051.1759), 1074 (M^++Na, 18), 1033 (M^+-H_2O, 12).

L-5, ^{1}H NMR δ: 5.856 (d, J=9.8 Hz, 1H, 9-H), 5.753 (m, 2H, 10-H & 11-H), 5.600 (d, J=4.5 Hz, 1H, 3-H), 5.390~5.425 (m, 1H, 1″-H), 5.297 (m, 1H, 19-H), 5.031 (d, J=7.0 Hz, 1H, 15-H), 4.630~4.864 (m, 3H, 1′-H & 8a-H_2), 4.408 (brs, 2H, 2×OH), 4.242 (s, 10H, 二茂铁环上的10个H), 4.159 (m, 1H, 5-H), 3.942 (s, 1H, 6-H), 3.658~3.903 (m, 6H, 13-H, 17-H, 5″-H, 5′-H, 3″-H & 3′-H), 3.428 (s, 6H, 2×O-Me), 3.164~3.239 (m, 4H, 4″-H, 4′-H, 2-H & 25-H), 2.513 (m, 1H, 12-H), 2.257~2.323 (m, 5H, 16-H_2, 24-H & 2″-H_2), 2.039 (d, 2H, 18-H_2), 1.869 (s, 3H, 4-Me), 1.296~1.735 (m, 14H, 20-H_2, 26-H, 27-H_2, 14-Me, 2″-H_2, 22-H_2 & 23-H_2), 1.148~1.273 (m, 9H, 5′-Me, 5″-Me & 12-Me), 0.792~1.024 (m, 9H, 28-Me, 26-Me & 24-Me); ^{13}C NMR δ: 173.701 (1-C), 171.162 (New, CO_2R), 139.671 (8-C), 137.981 (11-C), 137.825 (4-C), 135.023 (14-C), 124.754 (10-C), 123.847 (二茂铁环上的10个C), 120.394 (9-C), 118.358 (3-C), 118.086 (15-C), 98.504 (1″-C), 97.507 (21-C), 94.820 (1′-C), 81.806 (13-C), 80.405 (7-C), 79.375 (6-C), 79.260 (3′-C), 78.246 (3″-C), 77.125 (25-C), 76.705 (4″-C), 76.029 (4′-C), 68.645 (5″-C), 68.389 (17-C), 68.175 (8a-C), 67.730 (5-C), 67.243 (5′-C), 60.386 (19-C), 56.505 (O-Me), 56.414 (O-Me), 45.716 (2-C), 41.216 (20-C), 39.766 (12-C), 36.906 (16-C), 35.752 (26-C), 35.464 (18-C), 34.508 (2″-C), 34.269 (2′-C), 34.096 (24-C), 31.219 (22-C), 28.079 (23-C), 27.288 (27-C), 20.225 (12a-C), 19.920 (4a-C), 18.404 (6″-C), 17.703 (6′-C), 15.140 (14a-C), 14.184 (24a-C), 12.428 (26a-C), 12.099 (28-C); IR (KBr) ν: 3393, 2916, 1705, 1625, 1596, 1451, 1235, 1045, 890 cm^{-1}; MS (FAB) m/z (%): 1087 (M^+, 63), 1100 (M^++Na, 100).

L-6, ^{1}H NMR δ: 8.56~8.57 (d, J=4.0 Hz, 1H, Py-H), 7.79~7.81 (m, 1H, Py-H), 7.67~7.69 (d, J=8.0 Hz, 1H, Py-H), 7.35~7.38 (m, 1H, Py-H), 5.90 (brd, J=12.5 Hz, 1H, 9-H), 5.71~5.78 (m, 2H, 10-H & 11-H), 5.36~5.43 (m, 3H, 3-H, 1″-H, 19-H), 4.96 (d, J=7.1 Hz, 1H, 15-H), 4.66~4.80 (m, 3H, 1′-H & 8a-H_2), 4.27 (d, J=6.0

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Hz, 1H, 5-H), 4.18~4.21 (br, 2H, 2×OH), 4.02 (d, J=3.5 Hz, 1H, 6-H), 3.93~3.96 (d, J=6.1 Hz, 2H, 17-H &13-H), 3.65~3.83 (m, 4H, 5″-H, 5′-H, 3″-H &3′-H), 3.42 (s, 6H, 2×O-Me), 3.12~3.26 (m, 4H, 4″-H, 4′-H, 2-H &25-H), 2.55 (m, 1H, 12-H), 2.22~2.36 (m, 5H, 16-H_2, 24-H, 2″-H_2), 1.83~2.01 (m, 5H, 4-Me &18-H_2), 1.30~1.69 (m, 14H, 14-Me, 20-H_2, 26-H, 27-H_2, 2′-H_2, 22-H_2 &23-H_2), 1.05~1.26 (m, 9H, 5′-Me, 5″-Me & 12-Me), 0.79~0.96 (m, 9H, 28-Me, 26-Me &24-Me); IR (KBr) ν: 3455, 2918, 1677, 1627, 1528, 1382, 1249, 1081, 1001 cm^{-1}; MS (FAB) m/z (%): 980 (M^+, 26), 1003 (M^++Na, 13).

L-7, ^{1}H NMR δ: 8.42~8.44 (q, 1H, Py-H), 7.63~7.65 (q, 1H, Py-H), 7.28~7.31 (q, 1H, Py-H), 5.86~5.90 (d, J=10.3 Hz, 1H, 9-H), 5.74~5.78 (m, 2H, 10H &11-H), 5.34~5.42 (m, 3H, 3-H, 1″-H &19-H), 4.92~5.00 (d, J=7.3 Hz, 1H, 15-H), 4.72 (s, 1H, 1′-H), 4.64 (s, 2H, 8a-H_2), 4.28~4.32 (d, J=6.1 Hz, 1H, 5-H), 4.12 (m, 3H, 6-H, 17-H &13-H), 3.96 (brs, 2H, 2×OH), 3.60~3.70 (m, 4H, 5′-H, 5″-H, 3′-H &3″-H), 3.43 (s, 3H, O-Me), 3.42 (s, 3H, O-Me), 3.24~3.35 (m, 4H, 4′-H, 4″-H, 2-H &25-H), 2.59 (m, 1H, 12-H), 1.78~2.03 (m, 5H, 4-Me &18-H_2), 1.49~1.67 (m, 10H, 14-Me, 20-H_2, 26-H, 27-H_2 &2″-H_2), 1.01~1.32 (m, 13H, 22-H_2, 23-H_2, 5″-Me, 5′-Me & 12-Me), 0.80~0.94 (m, 9H, 28-Me, 26-Me &24-Me); IR (KBr) ν: 3416, 2946, 1732, 1621, 1578, 1447, 1115, 1045, 981 cm^{-1}; MS (FAB) m/z (%): 1014 (M^+, 6), 1037 (M^++Na, 23), 996 (M^+-H_2O).

L-8, ^{1}H NMR δ: 6.704 (s, 1H, Pyrazole-H), 5.842~5.869 (d, J=9.5 Hz, 1H, 9-H), 5.655~5.782 (m, 2H, 10-H &11-H), 5.602 (s, 1H, 3-H), 5.390~5.425 (d, J=3.6 Hz, 1H, 1″-H), 5.321~5.349 (m, 1H, 19-H), 4.968 (d, J=7.1 Hz, 1H, 15-H), 4.777 (m, 1H, 1′-H), 4.543~4.672 (m, 2H, 8a-H_2), 4.288 (d, J=6.0 Hz, 1H, 5-H), 4.124 (brs, 2H, 2×OH), 3.961 (d, J=6.6 Hz, 1H, 6-H), 3.933 (s, 1H, 13-H), 3.62~3.822 (m, 4H, 5′-H, 5″-H, 3′-H &3″-H), 3.421 (d, 6H, 2×O-Me), 3.356 (s, 1H, 2-H), 3.163~3.283 (m, 3H, 4′-H, 4″-H &25-H), 2.600~2.672 (m, 2H, Pz-CH_2), 2.512 (m, 1H, 12-H), 2.206~2.398 (m, 5H, 16-H_2, 24-H &2′-H_2), 1.872~2.010 (m, 5H, 20-H_2 & 4-Me), 1.808 (s, 3H, PzNMe), 1.642~1.778 (m, 5H, 18-H_2 &14-Me), 1.425~1.546 (m, 9H, 26-H, 27-H_2, 2″-H_2, 22-H_2, 23-H_2), 1.166~1.389 (m, 12H, 5′-Me, 5″-Me, 12-Me &Pz-CMe), 0.932 (t, 3H, 28-Me), 0.847 (d, J=6.8 Hz, 3H, 26-Me), 0.778 (d, J=6.8 Hz, 3H, 24-Me); ^{13}C NMR δ: 173.707 (1-C), 159.789 (New CO_2R), 139.578 (8-C), 138.324 (11-C), 138.171 (4-C), 135.280 (Pz-5-C), 135.171 (Pz-3-C), 133.483 (14-C), 124.918 (10-C), 120.582 (9-C), 118.747 (3-C), 118.318 (15-C), 109.662 (Pz-4-C), 98.787 (1″-C), 97.740 (21-C), 95.097 (1′-C), 82.071 (13-C), 81.467 (4′-C), 80.855 (7-C), 80.656 (6-C), 79.616 (3′-C), 79.471 (3″-C), 78.476 (25-C), 76.442 (4″-C), 76.045 (5″-C), 70.921 (PzNMe), 69.132 (17-C), 68.512 (8a-C), 68.405 (5-C), 67.985 (5′-C), 67.510 (19-C), 56.667 (OMe), 56.567 (OMe), 49.578 (Pz**C**H), 46.037 (2-C), 41.510 (20-C), 40.049 (12-C), 37.182 (16-C), 36.027 (26-C), 35.767 (18-C), 34.520 (2″-C), 34.337 (2′-C), 34.054 (24-C), 31.469 (22-C), 28.334 (23-C), 27.546 (27-C), 20.365 (12a-C), 19.799 (4a-C), 18.614 (6″-C), 17.865 (6′-C), 17.628 (24a-C), 15.349 (14a-C), 13.903 (PzCMe), 12.580 (26a-C), 12.313 (28-C); IR (KBr) ν: 3415, 2943, 1716, 1613, 1571, 1450, 1112, 1045, 981 cm^{-1}; MS (APCI) m/z (%): 1011.5 (M^+, 100, 计算值, 1011.264), 1034 (M^++Na, 8).

L-9, ^{1}H NMR δ: 5.946 (m, 1H, 9-H), 5.712~5.753 (m, 2H, 10-H &11-H), 5.410 (s, 1H, 3-H), 5.326 (m, 2H, 1″-H & 19-H), 5.201 (m, 1H, $NCHSO_2$), 4.987 (d, J=7.3 Hz, 1H, 15-H), 4.779 (d, J=3.6 Hz, 1H, 1′-H), 4.692 (s, 1H, $NCHCO_2$), 4.625~4.723 (m, 2H, 8a-H_2), 4.301 (d, J=6.1 Hz, 1H, 5-H), 4.143 (brs, 2H, 2×OH), 3.921~3.986 (m, 3H, 6-H, 17-H &13-H), 3.601 (m, 4H, 5′-H, 5″-H, 3′-H &3″-H), 3.472~3.490 (d, J=12.3 Hz, 2H, CH_2CO), 3.432 (s, 3H, OMe), 3.421 (s, 3H, OMe), 3.142~3.264 (m, 4H, 4′-H, 4″-H, 2-H &25-H), 2.638~2.677 (m, 5H, 12-H, 16-H_2 &2′-H_2), 2.233 (m, 1H, 24-H), 2.007 (d, J=3.5 Hz, 2H, 18-H_2), 1.932~1.956 (m, 3H, 4-Me), 1.715~1.830 (m, 2H, 20-H_2), 1.607~1.626 (3H, m, 14-Me), 1.450~1.500 (d, J=6.5 Hz, 6H, CMe_2), 1.338~1.427 (m, 9H, 26-H, 27-H_2, 2″-H_2,

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22-H_2 &23-H_2), 1.097 ~ 1.275 (m, 5′-Me, 5″-Me & 9H, 12-Me), 0.813 ~ 0.942 (m, 9H, 28-Me, 26-Me & 24-Me); IR (KBr) ν: 3318, 2911, 1703, 1621, 1566, 1445, 1261, 1045, 983 cm^{-1}. MS (APCI) *m/z* (%): 1090.1 (M^+, 46; 计算值, 1090.339), 1097 (M^+ + Li, 100), 1072 ($M^+ - H_2O$, 16).

L-10, ^1H NMR δ: 7.834 (s, 1H, ═NCH═), 7.734 (s, 1H, NCH═), 5.857 ~ 5.881 (d, *J* = 9.6 Hz, 1H, 9-H), 5.741 ~ 5.793 (m, 2H, 10-H & 11-H), 5.307 ~ 5.411 (m, 3H, 3-H, 1″-H & 19-H), 5.149 (m, 1H, $NCHSO_2$), 4.969 ~ 4.993 (d, *J* = 7.3 Hz, 1H, 15-H), 4.898 (d, *J* = 6.5 Hz, 2H, $TrCH_2$), 4.785 (s, 2H, 1′-H & $NCHCO_2$), 4.685 (s, 2H, 8a-H_2), 4.297 (d, *J* = 6.0 Hz, 1H, 5-H), 4.203 (brs, 2H, 2×OH), 3.946 ~ 3.986 (m, 2H, 6-H & 13-H), 3.754 ~ 3.867 (m, 3H, 17-H, 5′-H & 5″-H), 3.589 ~ 3.650 (m, 2H, 3′-H & 3″-H), 3.430 (s, 6H, 2× O-Me), 3.378 ~ 3.458 (m, 2H, CH_2CON), 3.153 ~ 3.287 (m, 4H, 4′-H, 4″-H, 2-H & 25-H), 2.524 (m, 1H, 12-H), 2.219 ~ 2.353 (m, 5H, 16-H_2, 24-H & 2′-H_2), 1.831 ~ 1.993 (m, 5H, 4-Me & 18-H_2), 1.648 ~ 1.770 (5H, 14-Me & 20-H_2), 1.361 ~ 1.569 (m, 9H, 26-H, 27-H_2, 2″-H_2, 22-H_2 &23-H_2), 1.126 ~ 1.334 (m, 12H, New Me, 5′-Me, 5″-Me &12-Me), 0.934 (t, 3H, 28-Me), 0.848 (d, *J* = 7.3 Hz, 3H, 26-Me), 0.797 (d, *J* = 7.3 Hz, 3H, 24-Me); IR (KBr) ν: 3332, 2919, 1706, 1623, 1569, 1450, 1266, 1045, 981 cm^{-1}; MS (APCI) *m/z* (%): 1156.6 (M^+, 16; 计算值, 1156.5501), 1163 (M^+ + Li, 45), 1174 ($M^+ + H_2O$, 100), 1180 (M^+ + Na), 1138 ($M^+ - H_2O$, 23).

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11 *FAO Plant Production and Protection Paper 21*, **1980**, pp. 49-53.

(A0106177 PAN, B. F.; DONG, L. J.)

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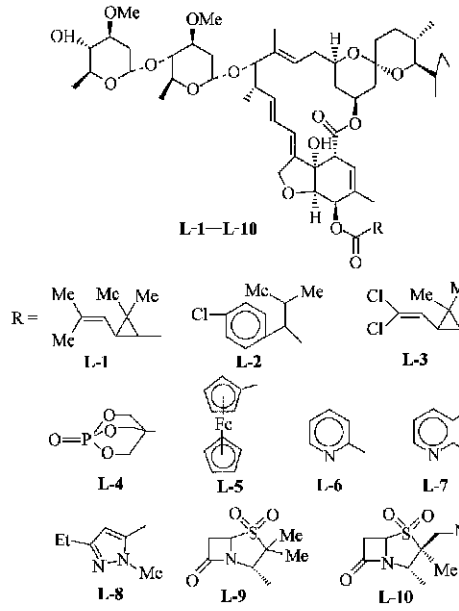
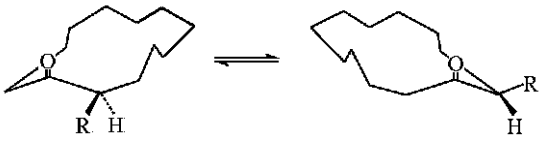
Synthesis and Bioactivity of 5-Ivermectin B_{1a} Esters



LIAO, Lian-An; LI, Zheng-Ming; FANG, Hong-Yun; ZHAO, Wei-Guang; FAN, Zhi-Jin; LIU, Gui-Long

Acta Chimica Sinica **2002**, *60* (3), 468

The Conformation of α-Monosubstituted Cyclododecanone

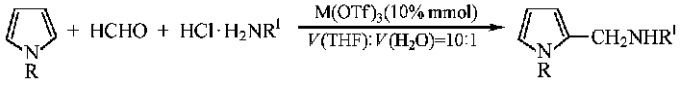


The ring skeleton of the preferred conformations of α-monosubstituted cyclododecanones is still [3333], with the carbonyl group present in the 2-C position. These molecules may adopt two different conformations in solution, the predominant α-side-*exo*-substituted and α-corner-*syn*-substituted conformation, which exist in dynamic equilibrium. The preferred conformation in the crystal is α-corner-*syn*-substituted conformation.

WANG, Dao-Quan; YANG, Xiao-Liang; WANG, Ming-An; LIANG, Xiao-Mei; YOU, Tian-Ba

Acta Chimica Sinica **2002**, *60* (3), 475

$M(OTf)_3$ Catalyzed Novel Mannich Reaction of *N*-Alkyoxycarbonylpyrrole or Thiophene, Formaldehyde and Primary Amine Hydrochloride

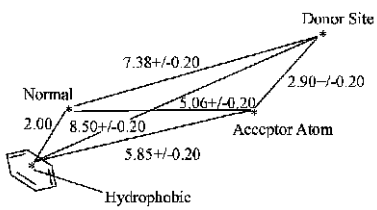


The novel Mannich of *N*-alkoxycarbonylpyrrole or thiophene, formaldehyde, primary amines hydrochlorides is catalyzed by $M(OTf)_3$ in aqueous media, $Y(OTf)_3$ was the best catalyst. The products are obtained in good yield under mild conditions.

ZHANG, Chuan-Xin; CHENG, Tie-Ming; LI, Run-Tao

Acta Chimica Sinica **2002**, *60* (3), 481

Design, Synthesis and Biological Activity Determination of New Type Photosystem Ⅱ Inhibitors



According to pharmacophore model, a series of new type photosystem Ⅱ inhibitors were designed, synthesized and characterized with element analysis, UV, IR and ^1H NMR. All compounds present the biological activities by Hill reaction.

LIU, Xiao-Lan; YANG, Xia; SUN, Ming; LIU, Xiao-Hong; ZHAO, Ru; MIAO, Fang-Ming

Acta Chimica Sinica **2002**, *60* (3), 487

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