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Synthesis of 4″-alkoxy avermectin derivatives using rhodium carbenoid-mediated O–H insertion reaction

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Abstract—4″-Alkoxy avermectin derivatives have been synthesized using O–H insertion reaction with ethyl diazoacetate in the presence of $Rh_2(OAc)_4$ as a catalyst.
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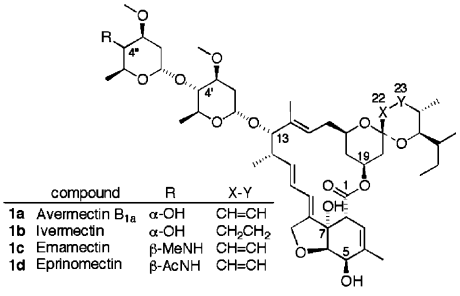
Avermectins are well known unique 16-membered ring macrolides with exceptionally potent anthelmintic, acaricidal, and insecticidal activities.[1] Avermectin B_1 (**1a**, Fig. 1), the major product from the culture broth of *Streptomyces avermitilis* and the most effective avermectin against insects and mites, has been commercialized for agricultural use.[2,3] 22,23-Dihydro avermectin B_1, named as ivermectin (**1b**), has also been commercially available as an anthelmintic drug for animals.[4] Recently ivermectin is also used in human for treatment of onchocerciasis,[5] strongyloidiasis,[6] and lymphatic filariasis.[7] Since the discovery of ivermectin, various avermectin derivatives have been synthesized to develop compounds having higher and broader spectra of activities.[8] In our research for new synthetic avermectins, we focused on chemical modification of the 4″-position on the L-oleandrose moiety to improve activities and pharmacokinetic profiles, because the introduction of acyloxy, amino, and thio groups at this moiety was found generally to induce preferable characteristics in their solubilities, distributions, chemical stabilities as well as activity spectra.[9,10] Among them, emamectin (**1c**) having *epi*-methylamino group at the 4″-position was developed as an agricultural insecticide.[11] Eprinomectin (**1d**) in which the 4″-hydroxy group is replaced by *epi*-acetylamino group exhibits potent endectocidal activity with minimal residues in milk, and is used for treatment of lactating dairy cattle parasites.[12] Although O-alkylation of the hydroxyl group at C4″ has already been reported,[13] applicability of the preceding methods to provide a variety of derivatives is limited. To develop avermectin derivatives modified at the 4″-position, we attempted O–H insertion reaction. The O–H insertion reaction of hydroxy compounds with diazo compounds in the presence of a catalyst is a powerful tool for the formation of alkoxy derivatives in organic chemistry.[14] However, very limited examples have been reported for the application to natural products, despite fact that the reactions normally proceed under mild condition giving good yields.[15] In this letter, we report the synthesis of new 4″-alkoxy avermectin derivatives by O–H insertion reaction of avermectin with ethyl diazoacetate in the presence of $Rh_2(OAc)_4$.



compound		R	X-Y
1a	Avermectin B_{1a}	α-OH	CH=CH
1b	Ivermectin	α-OH	CH_2CH_2
1c	Emamectin	β-MeNH	CH=CH
1d	Eprinomectin	β-AcNH	CH=CH

Figure 1. Structures of avermectins.

To prevent over reactions, 5-*O*-TBDMS-7-*O*-TMS-avermectin B_{1a} (**2a**) was prepared by (1) selective protection of the C5-hydroxyl group (TBDMSCl, imidazole, DMF, rt, 83%), (2) bisilylation of the C7 and C4″-hydroxyl groups (TMSCl, imidazole, DMF, rt),

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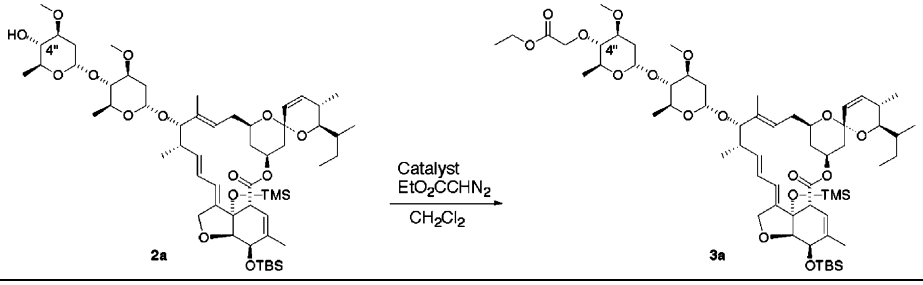
and (3) selective deprotection of the TMS group at 4″ (AcOH, THF–H_2O, rt, 92%, two steps). The O–H insertion reaction of **2a** with ethyl diazoacetate was attempted under several conditions, as shown in Table 1. $Rh_2(OAc)_4$ was a highly effective catalyst for the carbenoid reaction to give 4″-alkoxyl derivative (**3a**) in 62% yield (entry 1). However, longer reaction time and use of an excess ethyl diazoacetate resulted in the decrease of the isolated yield. Compound **3a** was easily purified by silica gel column chromatography and characterized by ^1H, ^{13}C NMR, and FABMS after desilylation.[16,17] We next attempted to change the ligand on rhodium (entries 2 and 3). $Rh_2(O_2CC_7H_{15})_4$ instead of $Rh_2(OAc)_4$ gave a modest yield, but $Rh_2(O_2CCF_3)_4$ with an electron-withdrawing ligand was not effective. Based on these results, we tried to examine the effects of electron-donating ligands (entries 4 and 5). Coordinating additives were found to improve the yield of O–H insertion reaction.[15a] Unfortunately, addition of tetramethyl thiourea (TMU) or dimethyl sulfide did not give better results. Although copper-catalyzed O–H insertion reaction is also been well known, treatment of **2a** with $Cu(OTf)_2$ resulted in poor conversion yielding unidentified side products (entry 6). Use of Lewis acids such as $BF_3{\cdot}Et_2O$ and $Sc(OTf)_3$ induced decomposition of the starting material (entries 7 and 8). Since O-alkylation according to the previous protocol (methyl iodoacetate, Ag_2O) did not work in our case,[13] the method using rhodium catalyst was expected to be more useful for synthesis of *O*-substituted avermectin derivatives.

We also examined the effect of other structural factors in avermectin derivatives on the O–H insertion reaction under the established optimal conditions (Table 2). For this purpose, suitably protected avermectins **2b–d** were synthesized. Under similar reaction conditions, ivermectin derivative **2b** and monosaccharide **2c** afforded alkoxy derivatives **3b** and **3c** in good yields. However, the reaction with aglycone **2d** did not proceed probably due to the steric hindrance at the C13-position.

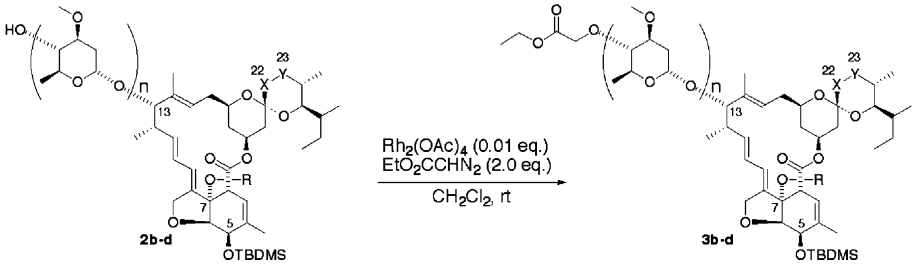
Table 1. The effect of catalysis on the O–H insertion reaction



Entry[a]	Condition	Yield (%)
1	$Rh_2(OAc)_4$ (0.02 equiv), rt, 4 h	62
2	$Rh_2(O_2CC_7H_{15})_4$ (0.01 equiv), rt, 2 h	42
3	$Rh_2(O_2CCF_3)_4$ (0.01 equiv), rt, 12 h	7 (99)[b]
4	$Rh_2(OAc)_4$ (0.01 equiv), TMU (0.1 equiv), rt, 12 h	11 (80)[b]
5	$Rh_2(OAc)_4$ (0.01 equiv), Me_2S (0.1 equiv), rt, 5 h	33 (70)[b]
6	$Cu(OTf)_2$ (0.05 equiv), rt, 12 h	18
7	$BF_3{\cdot}Et_2O$ (0.1 equiv), 0 °C, 2 h	Decomposed
8	$Sc(OTf)_3$ (0.02 equiv), rt, 1 min	Decomposed

[a] The reactions were carried out using 2.0 equiv of ethyl diazoacetate.
[b] Based on recovered starting material.

Table 2. The effect of structural factors of avermectin derivatives on the O–H insertion reaction



Compound	*n*	X–Y	R_1	R_2	Product	Yield (%)
2b	2	CH_2–CH_2	TBDMS	TMS	**3b**	67
2c	1	CH=CH	TBDMS	TMS	**3c**	57
2d	0	CH=CH	TBDMS	H	**3d**	No reaction

In conclusion, rhodium carbenoid mediated O–H insertion reaction has been shown to be useful for the synthesis of new avermectin derivatives. Now we are attempting to develop further modification of **3a**–**d**. In vitro and in vivo studies on new avermectin derivatives are in progress.

Acknowledgements

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16. A solution of **2a** (100 mg, 101 μmol) in dichloromethane (1 mL) containing rhodium acetate dimer (0.5 mg, 1.01 μmol) was stirred at room temperature for 10 min. To this solution was added a solution of ethyl diazoacetate (16 μL, 202 μmol) in dichloromethane (1 mL) dropwise, and the mixture was stirred. Evolution of nitrogen was observed. After stirring for 2 h, rhodium acetate dimer (0.5 mg, 1.01 μmol) was added again. The solvent was removed in vacuo. The crude product was purified by column chromatography on silica gel (5 g, hexane/ethyl acetate = 4:1) to provide **3a** (71.7 mg, 62%) as a white powder.
17. Selected data for deprotected **3a**, HRFABMS: calcd for $C_{52})H_{78}O_{16}Na$ $[M+Na]^+$ 981.5188, found 981.5234. ^1H NMR (270 MHz, $CDCl_3$) δ (ppm): 5.86 (m, 1H), 5.78–5.71 (m, 3H), 5.55 (dd, $J = 9.9$, 2.4 Hz, 1H), 5.42 (s, 1H), 5.38 (m, 1H), 5.32 (d, $J = 3.0$ Hz, 1H), 4.99 (m, 1H), 4.77 (d, $J = 3.0$ Hz, 1H), 4.71 (d, $J = 14.5$ Hz, 1H), 4.65 (d, $J = 14.5$ Hz, 1H), 4.37 (d, $J = 3.6$ Hz, 2H), 4.29 (br s, 1H), 4.21 (q, $J = 7.2$ Hz, 2H), 4.01 (br s, 1H), 3.97 (d, $J = 6.3$ Hz, 1H), 3.92 (br s, 1H), 3.88–3.78 (m, 3H), 3.69–3.55 (m, 2H), 3.48 (d, $J = 9.2$ Hz, 1H), 3.43 (s, 3H), 3.36 (s, 3H), 3.29 (d, $J = 2.2$ Hz, 1H), 3.20 (t, $J = 8.9$ Hz, 1H), 2.95 (t, $J = 8.9$ Hz, 1H), 2.51 (m, 1H), 2.38–2.18 (m, 6H), 2.01 (dd, $J = 12.5$, 3.7 Hz, 1H), 1.87 (s, 3H), 1.78 (dd, $J = 11.9$, 1.3 Hz, 1H), 1.62–1.44 (m, 7H), 1.31 (d, $J = 6.0$ Hz, 3H), 1.28 (t, $J = 7.2$ Hz, 3H), 1.24 (d, $J = 5.9$ Hz, 3H), 1.16 (d, $J = 6.9$ Hz, 3H), 0.95–0.85 (m, 10H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ (ppm): 173.6, 170.4, 139.5, 138.0, 137.9, 136.2, 135.1, 127.7, 124.6, 120.3, 118.2, 117.9, 98.3, 95.7, 94.7, 84.8, 81.7, 80.8, 80.3, 79.2, 79.0, 78.6, 74.8, 70.0, 68.4 (×2), 68.3 (×2), 67.6, 67.1, 60.6, 56.5, 56.2, 45.6, 40.4, 39.7, 36.6, 35.1, 34.8, 34.4, 34.2, 30.5, 27.4, 20.2, 19.9, 18.3, 17.9, 16.3, 15.1, 14.2, 12.9, 12.0. Deprotected **3c**, HRFABMS: calcd for $C_{45}H_{66}O_{13}Na$ $[M+Na]^+$ 837.4401, found 837.4397. ^1H NMR (270 MHz, $CDCl_3$) δ (ppm): 5.84 (1H, m), 5.76–5.68 (3H, m), 5.53 (1H, dd, $J = 9.9$, 2.3 Hz), 5.40 (1H, s), 5.37 (1H, m), 4.96 (1H, m), 4.74 (1H, d, $J = 3.3$ Hz), 4.65 (2H, br s), 4.37 (2H, d, $J = 2.0$ Hz), 4.27 (1H, m), 4.20 (2H, q, $J = 7.3$ Hz), 3.94 (1H, d, $J = 6.3$ Hz), 3.91 (1H, br s), 3.87 (2H, m), 3.70 (1H, m), 3.46 (1H, d, $J = 8.9$ Hz), 3.41 (3H, s), 3.27 (1H, d, $J = 2.0$ Hz), 2.94 (1H, t, $J = 9.1$ Hz), 2.47 (2H, m), 2.24 (4H, m), 2.00 (1H, dd, $J = 12.2$, 4.3 Hz), 1.85 (3H, s), 1.77 (1H, m), 1.56–1.41 (8H, m), 1.29 (3H, d, $J = 7.3$ Hz), 1.26 (3H, d, $J = 7.6$ Hz), 1.12 (3H, d, $J = 6.9$ Hz), 0.94–0.83 (m, 10H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ (ppm): 173.3, 170.5, 139.5, 138.0, 137.9, 136.2, 135.1, 127.7, 124.7, 120.4, 118.3, 118.0, 95.7, 94.8, 84.7, 82.0, 80.3, 79.1, 78.7, 74.8, 70.0, 68.4, 68.3 (×2), 67.6, 67.2, 60.6, 56.4, 45.6, 40.4, 39.7, 36.5, 35.1, 34.5, 34.2, 30.5, 27.4, 20.1, 19.9, 17.9, 16.3, 15.0, 14.2, 12.9, 12.0.