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A NOVEL SYNTHESIS OF AVERMECTIN B_{1a} FROM AVERMECTIN B_{2a} ‡

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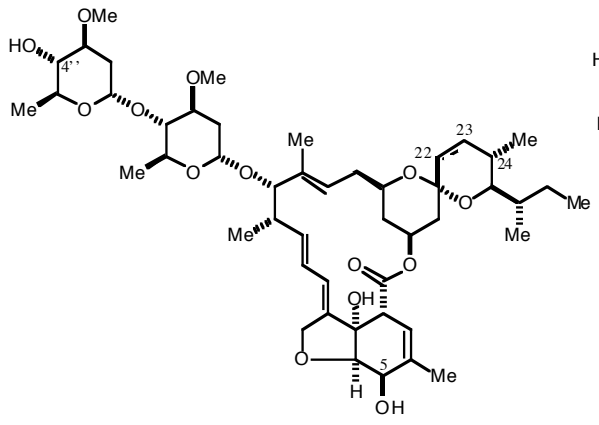
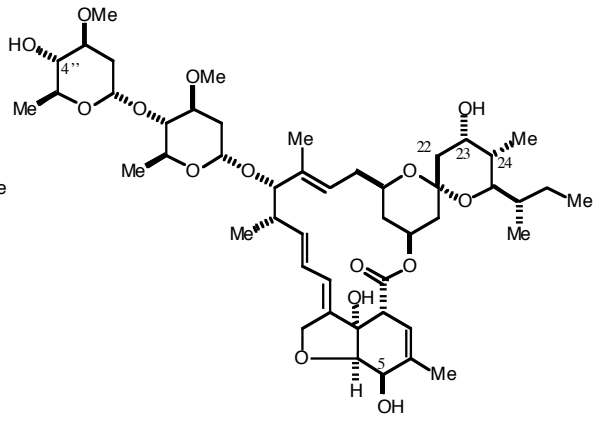
Abstract - The title synthesis was achieved *via* a four-step sequence of reactions including selective silylation of the $C_{4''}$- and the C_5-hydroxy groups, mesylation of the remaining C_{23}-hydroxy group, tetra-*n*-butylammonium oxalate-induced elimination, and deprotection of the silyl protecting groups.

Avermectin B_{1a} (**1**), a member of the avermectin family of 16-membered macrolides produced by the fermentation broth of *Streptomyces avermitilis*, exhibits remarkable biological properties including anthelmintic, miticidal, and insecticidal activities.[1,2] Avermectin B_{2a} (**3**) was also isolated from the same fermentation broth along with **1** in substantial amounts,[1,2] and it has been shown that **3** displays less potent anthelmintic activity than **1**.[3] Ivermectin (**2**),[4] a semi-synthetic derivative of **1** marketed by Merck Sharp

Figure 1. Structures of avermectin B_{1a} (**1**), ivermectin (**2**), and avermectin B_{2a} (**3**)



1 : avermectin B_{1a} ($\Delta^{22,23}$)
2 : ivermectin (22,23-dihydro)



3 : avermectin B_{2a}

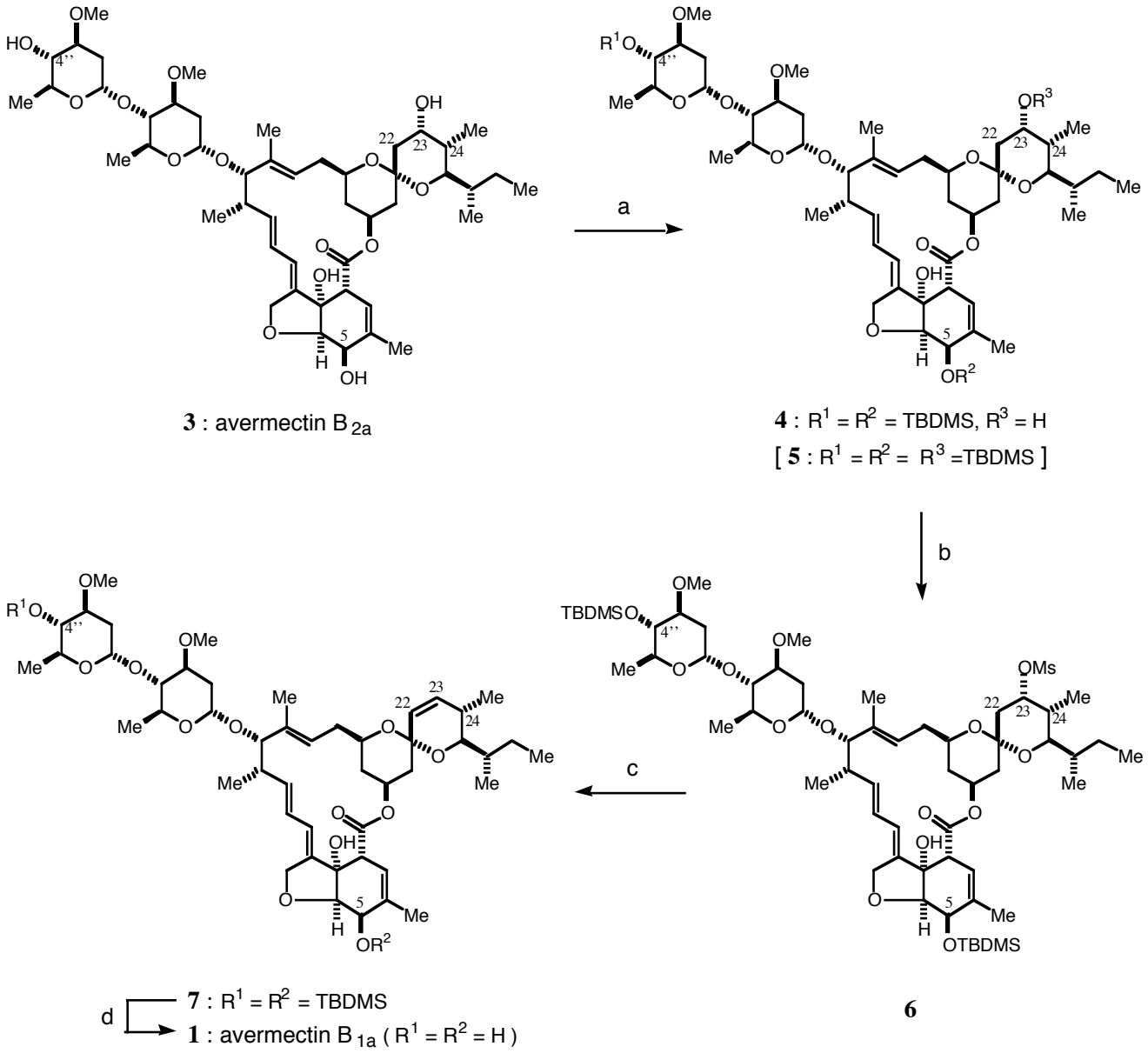
‡ This paper is dedicated to Professor Teruaki Mukaiyama of Science University of Tokyo on the occasion of his 73rd birthday.

and Dohme Co., is widely used as an anthelmintic agent in human and animal health.[5] **2** can be synthesized from **1** in a single step by selective hydrogenation of the C_{22},C_{23}-double bond employing Wilkinson's catalyst.[4] Since **1** is quite useful as medicinal, veterinarial, and agricultural products, it is an important objective to develop the method for the preparation of **1** starting from **3**. For this purpose, development of the method for regioselective dehydration of the C_{23}-hydroxy group in **3** leading to the C_{22},C_{23}-double bond is required. To date, two types of the syntheses of **1** from **3** have been reported by scientists at Merck Sharp and Dohme Co.;[6,7] one involves thiocarbonylation of the C_{23}-hydroxy group in **3** followed by pyrolysis (4% overall yield, 5 steps),[6] and the other involves cleavage of the C_{22}-C_{23} bond in **3** and subsequent reconstruction of the spiroketal portion (7% overall yield, 9 steps).[7] Herein, we wish to report a novel method for the synthesis of **2** from **3** (13% overall yield, 4 steps) which is obviously more efficient and facile than those reported.[6,7] The explored synthetic method features tetra-*n*-butylammonium oxalate-induced elimination[8] of the mesylate **6** (**6**→**7**) as the key step.

The synthesis commenced with selective protection of the two hydroxy groups at the $C_{4''}$- and the C_5-positions in avermectin B_{2a} (**3**) as shown in **Scheme 1**. Thus, **3** was treated with *tert*-butyldimethylsilyl chloride (TBDBSCl) (8.0 equiv) in the presence of triethylamine (8.8 equiv) in *N*,*N*-dimethylformamide (DMF)-dichloromethane (2:1)[9] according to the reported method[7a] with several improvements in the reaction conditions,[10] providing the desired disilyl ether (**4**) in 55% yield along with the trisilyl ether (**5**) (36%).[11] Although direct dehydration of the remaining C_{23}-hydroxy group in **4** was first attempted to obtain the desired $\Delta^{22,23}$-olefin (**7**) in a straightforward manner, all the dehydration reactions under standard conditions [*e.g.*, phosphorous oxychloride/pyridine, thionyl chloride/pyridine, triphenylphosphine/carbon tetrachloride, or (carbomethoxysulfamoyl)triethylammonium (Burgess reagent)[12]/benzene] gave no desired dehydration product (**7**), but resulted in almost complete decomposition of **4**. Therefore, we decided to look at the corresponding mesylate (**6**) in the hope that **6** would behave as a promising substrate for the delicate elimination. Toward this end, the C_{23}-hydroxy group in **4** was mesylated under the standard conditions to afford the mesylate (6) in 81% yield. With **6** in hand, we next investigated regioselective elimination leading to the C_{22},C_{23}-double bond. After several unsuccessful attempts,[13] the crucial elimination turned out to be effected by treating 6 with tetra-*n*-butylammonium oxalate [$(n\text{-}Bu_4N^+)_2(CO_2^{-})_2$][8,14] (10 equiv) in *tert*-butyl alcohol[15] at ambient temperature, leading to the formation of the requisite $\Delta^{22,23}$-olefin (**7**) as the sole product in 43 % yield along with thestarting material (**6**) (35% recovery).[16] In this reaction, the corresponding $\Delta^{23,24}$-olefin was not obtained at all. This result can be explained by the assumption that elimination leading to the C_{23},C_{24}-double bond is prohibited due to the moderate bulkiness of the base or/and its inherent weak basicity. The final phase remaining to complete the synthesis of **1** was the simultaneous removal of the two silyl protecting groups in **7**. Treatment of **7** with hydrogen fluoride-pyridine complex in acetonitrile at ambient temperature furnished avermectin B_{1a} (**1**) in 69% yield. The synthesized **1** was identical with a natural sample of **1**[9] in all spectroscopic properties (IR, ^{1}H-NMR, MS).

In summary, we have succeeded in developing a novel method for the synthesis of avermectin B_{1a} (**1**) starting from avermectin B_{2a} (**3**), which features regioselective elimination of the mesylate **6** (**6**→**7**) employing tetra-*n*-butylammonium oxalate as a base. The explored synthetic pathway which is obviously

Scheme 1. Synthesis of avermectin B_{1a} (**1**) from avermectin B_{2a} (**3**)



reagents and conditions : a) TBDMSCl, Et_3N, DMF-CH_2Cl_2 (2:1), 5°C, 67 h, 55% for **4**, 36% for **5** b) MsCl, pyridine, rt, 7 h, 81% c) (n-Bu_4N^+)$_2$(CO_2^-)$_2$, *tert*-BuOH, rt, 15 h, 43% (recovery of **6** : 35%) d) (HF)n·Py, MeCN, rt, 14 h, 69%

more efficient and facile than those previously reported, may be applicable to an industrial scale preparation of **1** from **3** due to operational simplicity and uses of inexpensive and less toxic reagents.

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9. This solvent system is crucial for this selective silylation. When only dichloromethane was used as a solvent,the reaction did not take place at all. On the contrary, only use of DMF provided the trisilyl ether (**5**) as a major product (**4** : 29%, **5** : 64%).
10. Selective silylation of the two hydroxy groups at the $C_{4"}$- and the C_5-positions in avermectin B_{2a} (**3**) has been reported [TBDMSCl (3.0 equiv), trietylamine (3.3 equiv), DMF-dichloromethane (2:1), rt, 16 h, 50% for **4**],[7a] therefore, the same reaction conditions were initially employed. However, the reaction gave no desired disilyl ether (**4**) but resulted in the formation of a hardly separable mixture of the $C_{4"}$- and the C_5-mono-*O*-silylated products in 15% combined yield along with a recovery of **3** (76%).
11. The disilyl ether (**4**) and the trisilyl ether (**5**) were readily separated by column chromatography on silica gel.
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13. When the mesylate (**6**) was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene(DBU), none of the desired elimination product (**7**) was obtained and the unreacted starting material (**6**) was recovered. Uses of other bases such as potassium *tert*-butoxide or aluminum oxide provided complicated mixtures of the products which contain no desired $\Delta^{22,23}$-olefin (**7**).
14. Preparation of tetra-*n*-butylammonium oxalate [$(n\text{-}Bu_4N^+)_2(CO_2^{-})_2$] : 10% Aqueous tetra-*n*-butylammonium hydroxide solution was carefully neutralized with oxalic acid employing phenol phthalein as an indicator. The solvent was evaporated and the residue was dried under reduce pressure, giving rise to tetra-*n*-butylammonium oxalate as a white solid.
15. Representative yields of the $\Delta^{22,23}$-olefin (**7**) and the recovered **6** obtained by using other standard solvents [$(n\text{-}Bu_4N^+)_2(CO_2^{-})_2$ (10 equiv), rt] were as follows : acetone (**7**:24%, **6**:22%), acetonitrile (**7**:15%, **6**:15%), tetrahydrofuran (**7**:11%, **6**:0%), 1,2-dimethoxyethane (**7**:21%, **6**:10%), benzene (**7**:37%, **6**:9%), toluene (**7**:30%, **6**:23%), dichloromethane (**7**:0%, **6**:96%), ethyl acetate (**7**:34%, **6**:48%), methyl alcohol (**7**:0%, **6**:97%), isopropyl alcohol (**7**:15%, **6**:64%).
16. Typical Procedure : 5,4"-Bis-*O*-(*tert*-butyldimethylsilyl)-23-*O*-(methanesulfonyl)avermectin B_{2a} (**6**) (10.5 mg, 8.8 μmol) was added to a stirred solution of tetra-*n*-butylammonium oxalate[14] (43.9 mg, 77 μmL) in *tert*-butyl alcohol (0.3 mL) at room temperature. After 15 h, the mixture was diluted with ethyl acetate (15mL). The organic layer was washed with water and brine, then dried over Na_2SO_4. Concentration of thesolvent *in vacuo* gave a residue, which was purified by preparative thin layer chromatography (EtOAc/hexane, 1:3) to give 5,4"-bis-*O*-(*tert*-butyldimethylsilyl)avermectin B_{2a} (**7**) (4.1 mg, 43%) as a colorless caramel along with **6** (3.7 mg, 35%).