Pergamon

*Tetrahedron Letters*, Vol. 35, No. 42, pp. 7797-7800, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01681-X

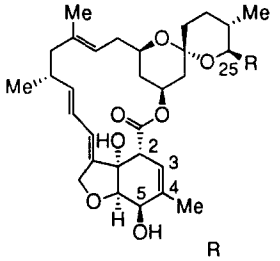
# Regeneration of the Milbemycin's $C_2$-$C_4$ Structural Arrangement from $\Delta^2$-Milbemycin

**Satoru Naito,* Yuka Owatari and Akio Saito**

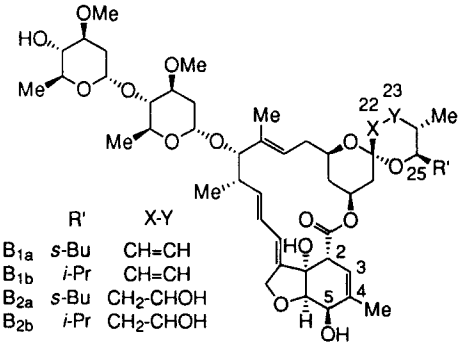
Medicinal Chemistry Research Laboratories, Sankyo Co,. Ltd.
1-2-58 Hiromachi, Shinagawa-ku, Tokyo 104, Japan

***Abstract:*** An efficient methodology for converting $\Delta^2$-milbemycin $A_4$ to milbemycin $A_4$ is described, whereby the $\Delta^2$-isomer is initially converted to the $C_2$ epimer which in turn is epimerized at $C_2$ to its natural configuration. The key transformation is a Dess-Martin type oxidation at $C_5$ of the $C_2$ epimer in order to enhance the stability of the $\Delta^3$-double bond and facilitate epimerization.

Milbemycins are a family of 16-membered ring macrolides which were first isolated in 1972 and later structurally elucidated by Sankyo chemists.[1] Shortly after this discovery, structurally-related avermectins were isolated by Merck scientists.[2] Since then, enormous efforts toward the total synthesis of these compounds have been made due to their structural uniqueness, and their potent anthelmintic, acaricidal and insecticidal activities. Various synthetic strategies for the substructures of milbemycins and avermectins, in particular the spiroketal and hexahydrobenzofuran portions, and the oleandrose disaccharide moiety, have been studied and devised, and this finally culminates in the syntheses of such natural products being reported from several groups.[3]



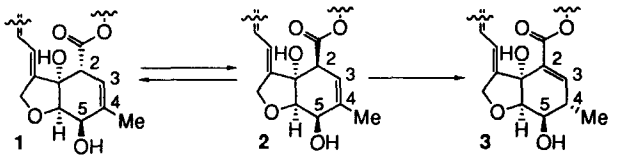
| | R |
|---|---|
| milbemycin $A_4$ (**1a**) | Et |
| milbemycin $A_3$ (**1b**) | Me |
| milbemycin D (**1c**) | *i*-Pr |



| | R' | X-Y |
|---|---|---|
| avermectin $B_{1a}$ | *s*-Bu | CH=CH |
| avermectin $B_{1b}$ | *i*-Pr | CH=CH |
| avermectin $B_{2a}$ | *s*-Bu | $CH_2$-CHOH |
| avermectin $B_{2b}$ | *i*-Pr | $CH_2$-CHOH |

Figure. 1

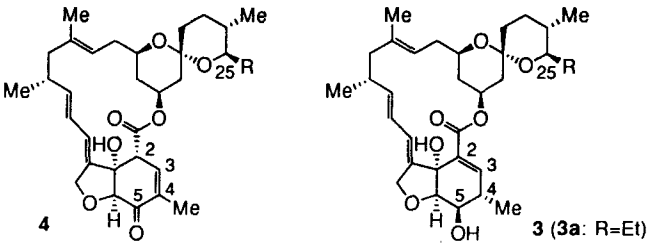
A major obstacle for accomplishing the total synthesis of milbemycins and avermectins has been to control the lability of both the $C_2$ center and the $\Delta^3$-double bond. Under basic conditions (0.05M KOH in MeOH-$H_2O$), for example, substrate **1** is apt to epimerize to the $C_2$ epimer **2** and thus irreversibly lead to the $\Delta^2$-isomer **3** (equation 1).[4]

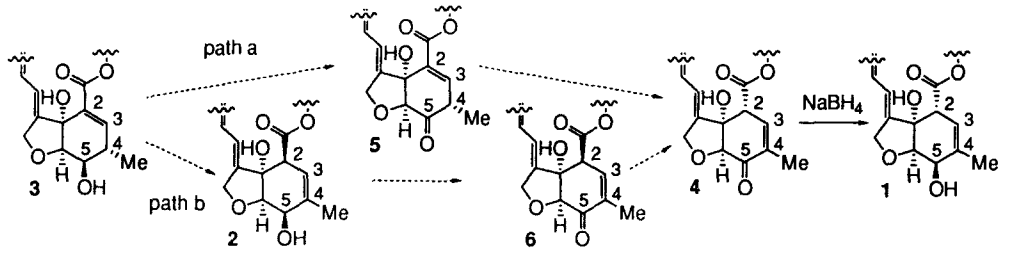


(1)

In the syntheses reported by Hanessian[5] and Danishefsky,[6] relatively stable $\Delta^2$-isomers were first synthesized, and deconjugation of the $\Delta^2$-double bond into the $\Delta^3$ position and subsequent epimerization at $C_2$ under equilibrium conditions[7] were carried out. White *et al.*[8] ingeniously constructed a $C_2$ epimer, which was similarly epimerized at $C_2$ to give a natural isomer. In all such cases, the lack of selectivity in these epimerization reactions is evident from the natural isomers being afforded merely in 30~40% yield, together with the corresponding starting materials and the $\Delta^2$-isomers which is in accordance with the equation 1. In order to obviate the problems of this procedure, the following strategies were developed: (1) generation of the $\Delta^3$-double bond by elimination of selenoxide at $C_4$,[9] (2) a sequence which involves the use of an intermediate with an exo double bond at $C_4$.[10] The former is moderately selective in the elimination reaction and the latter necessitates multiple steps for regenerating the $\Delta^3$-double bond. On the other hand, a somewhat straightforward approach to the problem, whereby the $C_2$-$C_4$ structural arrangement is correctly established from the onset, was disclosed by Hirama *et al.*,[11] albeit, the lactonization in the final stage suffers from a similar lability to that mentioned above. In this paper, a modified procedure for the $\Delta^2$-double bond migration-epimerization process is described, whereby introduction of a carbonyl group at $C_5$, by conjugative stabilization, holds the $\Delta^3$-double bond in place whilst the epimerization at $C_2$ can ensue.

In the course of our program to develop anthelmintics from milbemycins, 5-oxomilbemycin derivatives were utilized as the key intermediates for modifying the natural milbemycins.[12] The carbonyl group at $C_5$, which is a masking group of the original hydroxyl group, has its amenity in that it can be selectively reduced with $NaBH_4$ to provide the natural 5β-hydroxyl group.[13] Encouraged by this observation, **4** was identified

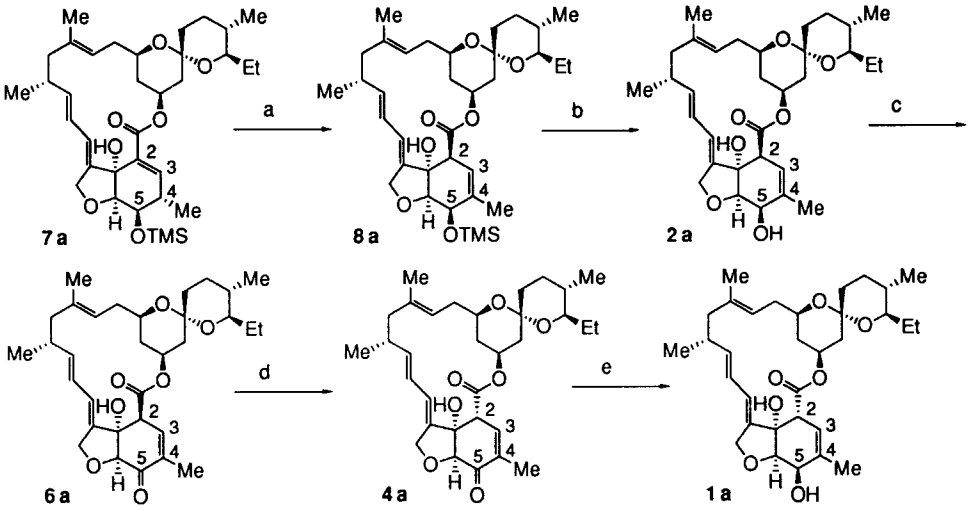





Scheme 1.

as an objective intermediate starting from $\Delta^2$-isomer **3**. It was assumed that conversion of the $C_5$ hydroxyl group of the $\Delta^2$-isomer **3** to a carbonyl group would induce the $\Delta^2$-double bond to migrate into conjugation with this newly-formed carbonyl group, and thus the $C_2$ center would attain its natural configuration under certain conditions (Scheme 1, path a). However, attempts to testify this assumption were thwarted. Various oxidation reactions (PCC, $MnO_2$, $SO_3$-pyridine, DMSO-TFAA and Dess-Martin periodinane) on the $\Delta^2$-isomer of milbemycin $A_4$ (**3a**)[14] failed to generate the corresponding ketone in our hands; instead only **3a** was recovered or decomposition products were identified.

Next, we focused on the $C_2$ epimer **2**. Similarly, it was expected that oxidation of **2** would provide the compound **6** suitable for the epimerization at $C_2$ (Scheme 1, path b). The $C_2$ epimer of milbemycin $A_4$ was prepared from 5-*O*-silyl-protected $\Delta^2$-isomer **7a**[14] by a modified Hanessian's procedure[7] as follows. Treatment of **7a** with 10 equiv of LDA in THF at -78°C for 10 min, and subsequent addition of a pre-cooled solution of acetic acid (15 equiv) in THF at -78°C over 5 min gave the epimer **8a** in 81% yield. This reaction was cautiously kept at -78°C, since an increase in reaction temperature, even during the quenching process, would give rise to a complex mixture. Use of a *t*-butyldimethylsilyl group (TBDMS) to protect the $C_5$ hydroxyl group was superseded by trimethylsilyl (TMS) protection since the TBDMS deprotection reaction was sluggish and accompanied with side reactions. Addition of 1N HCl in MeOH solution enabled facile deprotection of the epimer **8a** to give the 2-*epi*-milbemycin **2a** (94%, mp=139~141°C). Rather fortuitously, it was found that Dess-Martin periodinane[15] could efficiently oxidize the hydroxyl group at $C_5$ of **2a** to afford a compound which was assumed to be the 2-*epi*-5-oxo derivative **6a** by $^1H$ NMR.[16] As the compound **6a** was unstable, it was immediately subjected to epimerization. To our delight, treatment of the crude mixture with imidazole in $CH_2Cl_2$ at 0°C provided the 5-oxomilbemycin **4a**, which was confirmed by comparison of the $^1H$ NMR and HPLC data with an authentic sample,[13] and subsequent reduction of the carbonyl group at $C_5$ with $NaBH_4$ at -40°C gave the natural milbemycin **1a** (66% yield for three steps from **2a**).[17]




(a) LDA (10equiv), THF, -78°C, 10 min, then AcOH (15equiv); (b) HCl / MeOH, rt; (c) Dess-Martin periodinane (2 equiv), $CH_2Cl_2$, 0°C; (d) imidazole (0.11M) in $CH_2Cl_2$, 0°C; (e) $NaBH_4$ (excess), MeOH, -40~0°C.

Scheme 2.

In summary the procedure described above holds certain self-evident advantages over other reported methodologies for converting $\Delta^2$-isomers to the natural skeleton, although this procedure is to be extended to other milbemycins and derivatives in the avermectin series.

***References and Notes***


1. Aoki, A.; Fukuda, R.; Nakayabu, T.; Ishibashi, K.; Takeuchi, C.; Ishida, M. Japanese Patent, JP 7257058 (**1972**). Mishima, H.; Kurabayashi, M.; Tamura, C.; Sato, S.; Kuwano, H.; Saito, A.; Aoki, A. Abstract Papers 18th Symp. Chem. Natural Products, Kyoto, **1974**, pp. 309.
2. Albers-Schönberg, G.; Arison, B. H.; Chabala, J. C.; Douglus, A. W.; Escola, P.; Fisher, M. H.; Lusi, A.; Mrozik, H.; Smith, J. L.; Tolman, R. L. *J. Am. Chem. Soc.*, **1981**, *103*, 4216. Springer, J. P.; Arison, B. H.; Hirshfield, J. M.; Hoogsteen, K., *ibid.*, **1981**, *103*, 4221.
3. For reviews, see: Davies, H. G.; Green, R. H. *Natural Product Reports*, **1986**, *3*, 87. Davies, H. G.; Green, R. H. *Chem. Soc. Rev.*, **1991**, *20*, 211. Davies, H. G.; Green, R. H. *ibid.*, **1991**, *20*, 271. Blizzard, T.; Fisher, M. H.; Mrozik, H.; Shih, T. L.: Avermectins and Milbemycins. In *Recent Progress in the Chemical Synthesis of Antibiotics*; Lukacs, G.; Ohno, M. Eds.; Springer-Verlag: Berlin, 1990; pp. 65. Peak, S. A.; Smith, A. B., III.: Synthetic Routes to the Oxahydrindene Subunit of the Avermectin-Milbemycin Family of Antiparasitic Agents: A Review. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1993; Vol. 12, pp. 3.
4. Pivnichny, J. V.; Shim, J-S. K.; Zimmerman, L. A. *J. Pharm. Sci.*, **1983**, *72*, 1447. Pivnichny, J. V.; Arison, B. H.; Preiser, F. A.; Shim, J-S. K.; Mrozik, H. *J. Agric. Food Chem.*, **1988**, *36*, 826.
5. Hanessian, S.; Ugolini, A.; Dubé, D.; Hodges, P. J.; André, C. *J. Am. Chem. Soc.*, **1986**, *108*, 2776.
6. Danishefsky, S. J.; Selnick, H. G.; Armistead, D. M.; Wincott, F. E. *J. Am. Chem. Soc.*, **1987**, *109*, 8119.
7. Fraser-Reid, B.; Wolleb, H.; Faghih, R.; Barchi, J. Jr. *J. Am. Chem. Soc.*, **1987**, *109*, 933. Hanessian, S.; Dubé, D.; Hodges, P. J. *ibid.*, **1987**, *109*, 7063.
8. White, J. D.; Bolton, G. L. *J. Am. Chem. Soc.*, **1990**, *112*, 1626.
9. Armstrong, A.; Ley, S. V. *Synlett*, **1990**, 323. Martin, D. D.; Grice, D.; Kolv, H. C.; Ley, S. V.; Madin, A. *ibid.*, **1990**, 326. Armstrong, A.; Ley, S.; V. Madin, A.; Mukherjee, S. *ibid.*, **1990**, 328. Ford, M. J.; Knight, J. G.; Ley, S. V.; Vile, V. *ibid.*, **1990**, 331.
10. Fraser-Reid, B.; Barchi, J. Jr.; Faghih, R. *J. Org. Chem.*, **1988**, *53*, 923.
11. Hirama, M.; Noda, T.; Yasuda, S.; Ito, S. *J. Am. Chem. Soc.*, **1991**, *113*, 1830.
12. Saito, A.; Naito, S.; Kobayashi, M.; Tsuchiya, M.; Toyama, T.; Kaneko, S.; Nanba, T.; Morisawa, Y. *J. Antibiot.*, **1993**, *46*, 1252.
13. Ono, M.; Mishima, H.; Ide, J.; Muramatsu, S. *J. Antibiot.*, **1983**, *36*, 980. Tsukamoto, Y.; Sato, K.; Mio, S.; Sugai, T.; Yanai, T.; Muramatsu, S.; Nakada, Y.; Ide, J. *Agric. Biol. Chem.*, **1991**, *55*, 2615.
14. **3a** and **7a** were prepared from milbemycin $A_4$ by the following reactions: (1) protection of the $C_5$ hydroxyl group of **1a** (TBDMSCl, imidazole, DMF), (2) conjugation (DBU, toluene), (3) deprotection (10% TsOH, MeOH) to give **3a**, and (4) protection of the $C_5$ hydroxyl group (TMSCl, $Et_3N$, $CH_2Cl_2$) to give **7a**. For conjugation, see: Selnick, H. G.; Danishefsky, S. J. *Tetrahedron Lett.*, **1989**, *28*, 4955.
15. Dess, B. D.; Martin, J. C. *J. Org. Chem.*,**1983**, *48*, 4155.
16. The reaction was monitored by TLC (RP-18, $F_{254}$). Partial $^1H$ NMR data for **6a**: (270MHz, $CDCl_3$) $\delta$ 6.68 (1H, m, $H_3$), 6.03 (1H, br d, $J$=10.6Hz, $H_9$), 5.68 (1H, dd, $J$=10.6, 15.2Hz, $H_{10}$), 5.53 (1H, dd, $J$=7.9, 15.2Hz, $H_{11}$), 5.38~5.50 (1H, m, $H_{19}$), 4.91 (1H, br d, $J$=8.6Hz, $H_{15}$), 4.64 (1H, dd, $J$=2.0, 15.2Hz, $H_{8a}$), 4.33 (1H, s, $H_6$), 4.28 (1H br d, $J$=15.2Hz, $H_{8a'}$), 3.90 (1H, m, $H_2$), 3.61~3.70 (1H, m, $H_{17}$), 3.08 (1H, dt, $J$=2.6, 9.2Hz, $H_{25}$).
17. Examination of the product mixture by HPLC on a YMC ODS AM-312 column with UV detection at 254 nm (95:5 $CH_3CN$-$H_2O$, 1ml/min) revealed that milbemycin $A_4$ (**1a**), $C_2$ epimer **2a** and $\Delta^2$-isomer **3a** were present in the ratio of 91:6:3.


(*Received in Japan* 13 *May* 1994; *accepted* 18 *July* 1994)