## Communications to the Editor

[Chem. Pharm. Bull. 35(6)2598—2601(1987)]

# TOTAL SYNTHESIS OF ESTERS OF AK-TOXIN II AND AF-TOXIN IIc STARTING FROM VITAMIN C AS A CHIRAL MATERIAL

Hiroshi Irie,*[,a] Kohei Matsumoto,[a] Takao Kitagawa,[a] Yong Zhang,[a] Tamio Ueno,[b] Tadakazu Nakashima,[b] and Hiroshi Fukami[b]

Faculty of Pharmaceutical Sciences, Nagasaki University,[a] Nagasaki, 852 Japan and Pesticide Research Institute, Faculty of Agriculture, Kyoto University,[b] Sakyo-ku, Kyoto 606 Japan

Total synthesis of the methyl esters of AK-toxin II and AF-toxin IIc, host-specific toxins to the susceptible cultivars Japanese pear and strawberry, was accomplished in optically active forms using vitamin C as a chiral material.

KEYWORDS —— phytotoxicity; host-specific toxin; vitamin C; chiral synthon; isoleucine; Wadsworth-Emmons reaction; Mitsunobu reaction

Previously, we reported the synthesis of the congeners of AK-toxin II[1] and AF-toxin IIc[2] methyl esters and revealed two chiral centers of the trienoic acid moiety of AF-toxin IIc to be at least of the $C_8$(R) and $C_9$(S) configuration.[3] However, the stereochemistry of the 2-hydroxy-3-methylpentanoic acid moiety of the toxin remained to be elucidated.[4] In continuing the synthesis of the toxins, AK- and AF-toxins produced by *Alternaria kikuchiana* and *A. alutanata*, respectively, we report total synthesis of the methyl esters (2) and (4) of AK-toxin II (1) and AF-toxin IIc (3) in optically active forms from vitamin C as a chiral starting material.

As indicated previously,[3] vitamin C is easily converted to the aldehyde (5) The known all-*trans*-trienoic ester (7)[3] was obtained, though as a minor product, in one step by a Wadsworth-Emmons reaction of (5) with methyl 4-dimethylphosphonocrotonate. Unexpectedly, the major product of the above reaction was the cyclic compound (6) produced by participation of two double bonds in the reaction intermediate and by a hydrogen rearrangement as depicted in Chart 1. On the other hand, treatment of (5) with methyl 4-triphenylphosphoniumcrotonate gave the *cis*- (8) and the *trans*-trienoic acid ester (7) in 85% yield in 3:1 ratio. Oxidation of (8) with *m*-chloroperbenzoic acid gave two diastereoisomeric oxides (9) and (10) in 38% and 43% yield, respectively. The structures of these oxides were determined by comparing their $^1$H-NMR spectral data with those of natural AK-toxins and their congeners.[3]

De-protection of the silyl group in the oxide (9) with tetrabutylammonium fluoride gave the alcohol (11) in good yield. The alcohol was esterified with N-acetyl-L-phenylalanine and dicyclohexylcarbodiimide in the presence of 4-pyrrolidinopyridine[5] to give a mixture of AK-toxin II methyl ester (2)[6] and its epimer

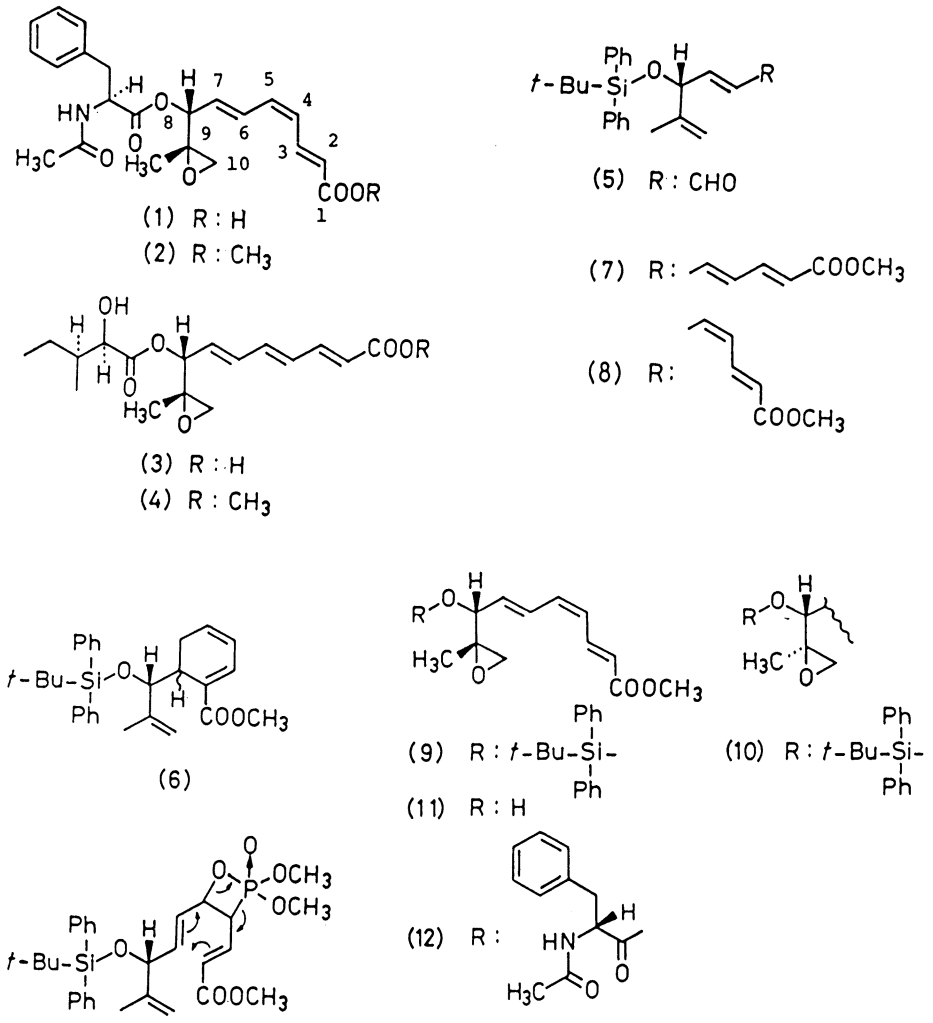
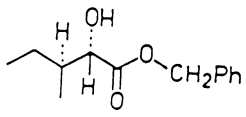



Chart 1

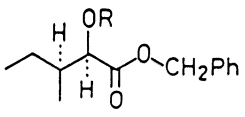
(12). This was a result of an inevitable racemization caused by activation of the carboxylic acid group of N-acetylphenylalanine. The stereochemistry of the α-carbon of phenylalanine in the esters (2) and (12) was confirmed by the L- and D-amino acid determination method.[7] The synthetic AK-toxin II methyl ester (2) was identical with the natural one in all respects, confirming the total synthesis of the toxin methyl ester from vitamin C as a chiral starting material.[8]

Next, we focused our attention on the total synthesis of AF-toxin IIc methyl ester (4). Treatment of the hydroxy-ester (13),[3] $[\alpha]_D^{27}$ -11.8° (c=1.0, EtOH),

with formic acid and diethyl azodicarboxylate (Mitsunobu reaction) gave the formyl ester (14), $[\alpha]_D^{23}$ +23.3° (c=1.2, $CHCl_3$), which, under mild alkaline hydrolysis, gave the hydroxy-ester (15), $[\alpha]_D^{23}$ +9° (c=1.1, EtOH) in 80% yield. Protection of a hydroxyl group as *tert*-butyldiphenylsilyl ether followed by hydrogenation gave the acid (16), $[\alpha]_D^{22}$ +18.5° (c=1.0, EtOH). The all-*trans*-ester (17)[3] was subjected to acylation with the acid (16) to furnish the ester (18) in 75% yield without racemization by Hassner and Alexanian's method.[5] Treatment of (18) with tetrabutylammonium fluoride in tetrahydrofuran gave AF-toxin IIc methyl ester in80% yield. The $^1$H-NMR spectrum[9] (400MHz in $CDCl_3$) showed signals identical with those of the reported values,[2] thus confirming the synthesis of AF-toxin IIc methyl ester.[10]

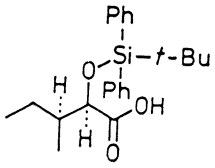


(13)

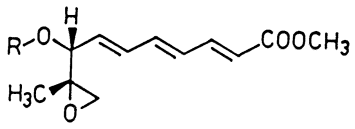


(14) R : CHO

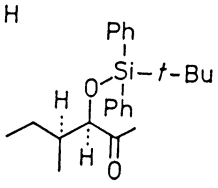
(15) R : H



(16)



(17) R : H



(18) R :

Chart 2

ACKNOWLEDGEMENT This study was supported in part by a Grant in Aid for Scientific Research (No. 61571007) from the Ministry of Education, Science and Culture of Japan.

REFERENCES AND NOTES

1) T. Nakashima, T. Ueno, and H. Fukami, *Tetrahedron Letters*, 23, 4469 (1982); T. Nakashima, T. Ueno, H. Fukami, T. Taga, H. Masuda, K. Osaki, H. Otani, K. Kohmoto, and S. Nishimura, *Agric. Biol. Chem.*, 49, 807 (1985); H. Otani, K. Kohmoto, and S. Nishimura, T. Nakashima, and H. Fukami, *Ann. Phytopath. Soc. Japan*, 51, 285 (1985).

2) S. Nakatsuka, K. Ueda, T. Goto, M. Yamamoto, S. Nishimura, and K. Kohmoto, *Tetrahedron Letters*, 27, 2753 (1986).

3) H. Irie, K. Matsumoto, and Y. Zhang, *Chem. Pharm. Bull.*, 34, 2668 (1986).

4) When we synthesized the compound, which had an entire carbon skeleton and functionalities corresponding to AF-toxin IIc and was toxic to the leaves of Nijisseiki (japanese pear), we thought the synthesis of the toxin had been achieved. Then we requested the spectroscopic data from the Nagoya group but did not receive the data. After our paper[3] indicating the stereostructure of AF-toxin IIc was accepted, the Nagoya group reported the $^1$H-NMR data of AF-toxin IIc methyl ester. Then we realized our compound was not identical with the natural toxin, since the chemical shifts of the primary and secondary methyl groups of our compound were quite different from those of genuine toxin. Because of its toxicity, the synthetic compound was thought to have the right stereostructure in the part of the trienoic acid moiety but the wrong configuration in the 2-hydroxy-3-methylpentanoic acid part.

5) A. Hassner and V. Alexanian, *Tetrahedron Letters*, 1978, 4475.

6) $^1$H-NMR ($\delta$) ($CDCl_3$) 1.31 (3H, s), 2.01 (3H, s), 2.61 (1H, d, $J$=4.6Hz), 2.75 (1H, d, $J$=4.6Hz), 3.12 (2H, d, $J$=6.2Hz), 3.77 (3H, s), 5.27 (1H, d, $J$=7.7Hz), 5.70 (1H, dd, $J$=15.0 and 7.7Hz), 5.92 (1H, broaded and overlapped on $\delta$ 5.95 signal, *NH*), 5.95 (1H, d, $J$=15.4Hz), 6.20 (1H, t, $J$=11.5Hz), 6.29 (1H, t, $J$=11.5Hz), 6.84 (1H, dd, $J$=15.0 and 11.5Hz), 7.08 (2H, dd, $J$=7.9 and 1.6Hz), 7.35-7.20 (3H, m), 7.70 (1H, dd, $J$=15.4 and 11.5Hz).

7) C.R. Shoaf, K.J. Isselbacher, and W.D. Heizer, *Anal. Biochem.*, 61, 72 (1974).

8) To our knowledge, there have been only two reports concerning the synthesis of natural products using vitamin C as a chiral starting material. M.E. Jung and T.J. Shaw, *J. Am. Chem. Soc.*, 102, 6304 (1980); C.C. Wei, S.D. Bernardo, J.P. Tengi, J. Borgese, and M. Weigele, *J. Org. Chem.*, 50, 3462 (1985).

9) The $^1$H-NMR data of synthetic AF-toxin IIc methyl ester; (the reported data are indicated in parenthesis) ($\delta$) ($CDCl_3$), 0.85 (3H, d, $J$=7.0Hz), (0.87); 0.98 (3H, t, $J$=7.4Hz), (0.97); 1.36 (2H, m) (1.36); 1.36 (3H, s), (1.36); 1.84 (1H, m), (1.84); 2.61 (1H, d, $J$=5.9Hz, OH), (2.60); 2.63 (1H, d, $J$=4.8Hz), (2.62); 2.79 (1H, d, $J$=4.8Hz), (2.78); 3.76 (3H, s), (3.75); 4.23 (1H, dd, $J$=2.9 and 5.9Hz), (4.21); 5.35 (1H, d, $J$=7.3Hz), (5.34); 5.82 (1H, dd, $J$=7.3 and 14.8Hz), (5.82); 5.94 (1H, d, $J$=15.4Hz), (5.94); 6.38 (1H, dd, $J$=11.0 and 14.5Hz), (6.38); 6.43 (1H, dd, $J$ =10.8 and 14.8Hz), (6.43); 6.53 (1H, dd, $J$=10.8 and 14.5Hz), (6.53); 7.29 (1H, dd, $J$=11.0 and 14.4Hz), (7.29).

10) The $^1$H-NMR data of AF-toxin IIc methyl ester were not available, when our paper (ref. 3) was in press.

(Received March 28, 1987)