Communications to the Editor

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AN APPROACH TO A SYNTHESIS OF THE HOST-SPECIFIC TOXINS AK-TOXIN I AND II, STARTING FROM VITAMIN C AS A CHIRAL MATERIAL

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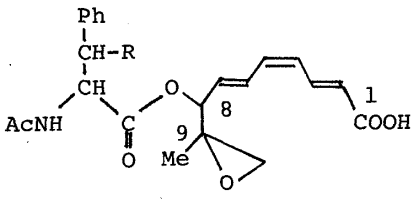
An approach to the synthesis of AK-toxin I and II starting from Vitamin C was investigated. During the course of the approach, the stereostructure of the trienoic acid part of the toxins were revealed to be 8(R),9(S)- or 8(S),9(R)-9,10-epoxy-9-methyl-8-hydroxy-2E,4Z,6E-decatrienoic acid.

KEYWORDS——host-specific toxin; Vitamin C; absolute configuration; AK-toxin

The fungus, *Alternaria kikuchiana* Tanaka, produces the host-specific toxins AK-toxin I and II, which cause the black spot disease of Japanese pear, *Pyrus serotina* Rehder *var. culta*, cv. Nijisseiki.[1] The structures of the toxins have been elucidated by our Kyoto group to be (1) and (2) without stereochemistry at the asymmetric carbons of their trienoic acid part.[2] We aim to synthesize these toxins and their congeners in optically active forms by a stereoselective method. This report describes an approach to the synthesis of the toxins starting with Vitamin C[3] and an inference regarding the configuration of two asymmetric carbons.

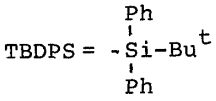
Oxidation of 5,6-isopropylideneascorbic acid with potassium permanganate under carbon dioxide[4] gave the potassium salt (3) ($[\alpha]_D^{22}$ +24.8° (c=2.6 water)), which was converted to the methyl ester (4)[5] ($[\alpha]_D^{21}$ +21.0° (c=2.4 acetone)) by treatment with one molar equivalent of methanolic hydrochloric acid followed by diazomethane at -78°C in 63% yield. The Grignard reaction of (4) with MeMgI gave the diol (5) ($[\alpha]_D^{25}$ +3.4° (c=0.9 EtOH)). Bezoylation of (5) in the usual way gave the mono-benzoate (6) ($[\alpha]_D^{24}$ -10.1° (c=1.0 EtOH)) which, by treatment with thionyl chloride in pyridine, gave the olefin (7) ($[\alpha]_D^{24}$ -15.8° (c=1.1 EtOH)) in 80% yield. Alkaline hydrolysis of the ester group in (7) and re-protection of the resulting hydroxyl group with the *tert*-butyl-diphenylsilyl (TBDPS) group yielded the olefin-silyl-ether (8) ($[\alpha]_D^{20}$ -21.0° (c=1.0 EtOH)) in 72% yield. Treatment of the ether (8) with trifluoroacetic acid in methanol gave the glycol (9) ($[\alpha]_D^{21}$ -18.6° (c=1.0 EtOH)) in 90% yield. Oxidation of the glycol (9) with periodic acid gave the aldehyde (10) in 95% yield. The Wadsworth-Emmons reaction of (10) with triethyl phosphonoacetate and sodium hydride in benzene afforded the *trans*-ester (11) ($[\alpha]_D^{22}$ -29.0° (c=1.0 EtOH)) in 90% yield. Epoxidation of the ester with *m*-chloroperbenzoic acid in methylene chloride at room temperature

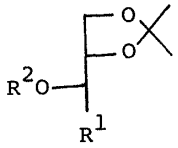
overnight gave a mixture consisting of the stereoisomers (12) ($[\alpha]_D^{22}$ -26.7° (c=1.3 EtOH)) and (13) ($[\alpha]_D^{22}$ -28.0° (c=1.2 EtOH)) in 40% and 50% yield, respectively, both of which were separated in pure form by preparative thin layer chromatography on silica gel plate.[6]



(1) R=Me

(2) R=H





(3) $R^1=CO_2^- K^+$, R^2=H

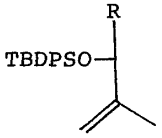
(4) $R^1=CO_2Me$, R^2=H

(5) R^1=  , R^2=H

(6) R^1= , R^2=COPh

(7) R^1=  , R^2=COPh

(8) R^1=  , R^2=TBDPS



(9) R= 

(10) R=CHO

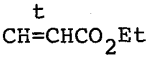
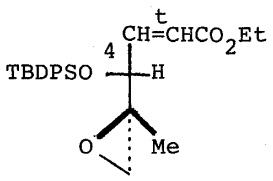
(11) R= 

Chart 1



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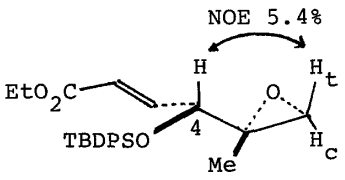
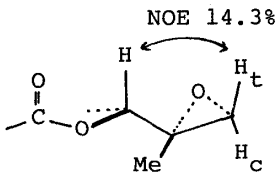
(12)

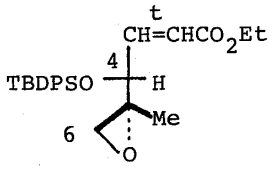


(12')

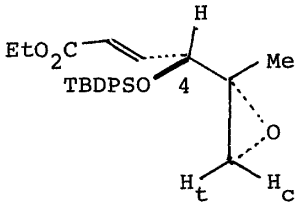
(long-range coupling between Me-protons and H_t)



(14)



(13)



(13')

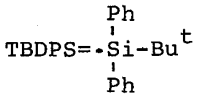


Chart 2

In one of the plausible conformations of the epoxide (12) (4R,5S), in which two oxygen groups, the epoxy and siloxy groups, are separate from each other, a close proximity of the carbinyl proton (C_4-H) and one of the methylene protons (C_6-H_t) of the epoxide moiety is expected, while none of methylene protons of the epoxide moiety is in close proximity to the carbinyl proton in the same type of conformation of the epoxide (13) (4R,5R). Actually, one of the epoxides (12), which showed in the ^{1}H-NMR spectrum a pattern similar to that (partly shown as (14)) of AK-toxins, exhibited on irradiation of the carbinyl proton a nuclear Overhauser effect (NOE) (5.4% enhancement) on C_6-H_t as indicated in Chart 2.

Based on the above findings, the stereostructure of the two chiral centers of the trienoic acid moiety of AK-toxins is thought to be at least either 8R,9S or 8S,9R.[7)]

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REFERENCES AND NOTES

1) S. Tanaka, Mem. Coll. Agr. Kyoto Univ., 28 (Phytopath. Series No. 6), 1 (1933).

2) T. Nakashima, T. Ueno, and H. Fukami, Tetrahedron Lett., 23, 4469 (1982).

3) To our knowlege, the synthesis of (-)-γ-amino-β-hydroxybutyric acid (GABOB) is the only successful synthesis using Vitamin C as a chiral starting material: M.E. Jung and T.J. Shaw, J. Am. Chem. Soc., 102, 6304 (1980).

4) T. Reichstein, A. Grüssner, and W. Bosshard, Helv. Chim. Acta, 18, 602 (1935).

5) All the compounds cited here had the expected spectral properties in accord with the indicated structures.

6) ^{1}H-NMR spectra ($CDCl_3$) δ: The epoxide (12); 1.10 (9H, s), 1.26 (3H, s), 1.30 (3H, t, J=7.0Hz), 1.86 (1H, d, J=4.9Hz), 2.21 (1H, d, J=4.9Hz), 3.86 (1H, d.d, J=4.4 and 1.5Hz), 4.02 (2H, q, J=7.0Hz), 6.14 (1H, d.d, J=15.7 and 1.5Hz), and 6.95 (1H, d.d, J=15.7 and 4.4Hz): The epoxide (13); 1.12 (9H, s), 1.26 (3H, t, J=7.3Hz), 1.35 (3H, s), 2.57 (2H, s), 3.96 (1H, d.d, J= 5.3 and 1.5Hz), 4.14 (2H, q, J=7.3Hz), 5.83 (1H, d.d, J=15.7 and 2.3Hz), and 6.74 (1H, d.d, J=15.7 and 5.3Hz).

7) Recently the Kyoto group revealed the absolute configuration of AK-toxin I by X-ray crystallographic determination, confirming that the configuration of the two chiral centers of trienoic acid part of toxins are 8R and 9S.

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