TOTAL SYNTHESIS OF AK-TOXIN II

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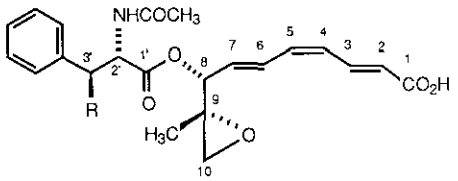
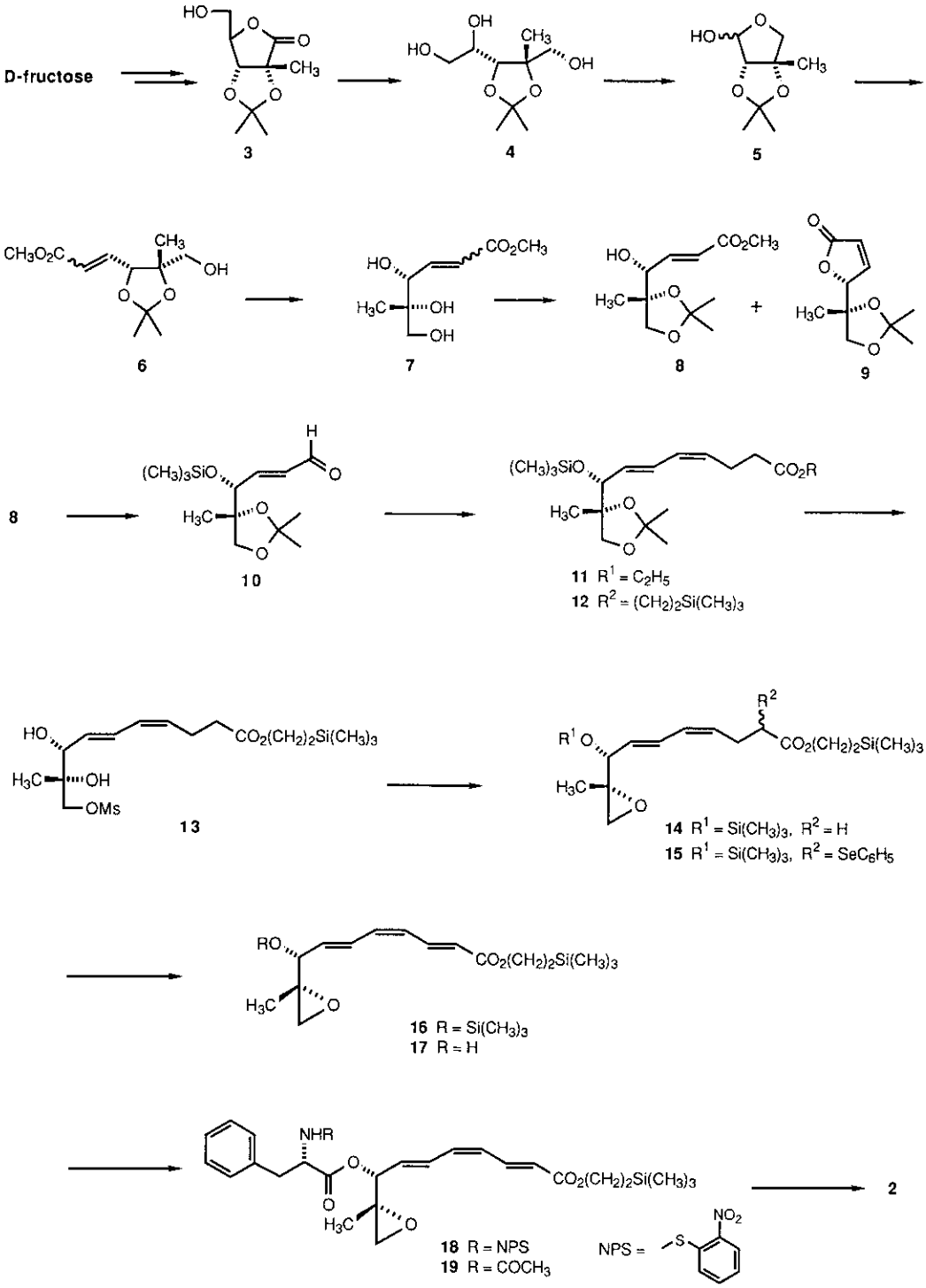
Abstract-Total synthesis of AK-toxin II, a host-specific phytotoxic metabolite, is described using D-fructose as starting material.

AK-toxins I and II are host-specific phytotoxic metabolites produced by *Alternaria alternata* Japanese pear pathotype.[1] This fungus is characteristically infectious to *Pyrus serotina* Rehder var. *culta* (cv. Nijisseiki) but not to other resistant agricultural species of Japanese pear. Nakashima and co-workers isolated AK-toxins I and II from a culture broth of the fungus and identified them as the host-specific toxins.[1] The chemical structure of AK-toxin I was determined as (8R,9S,2'S,3'S)-8-(2'-acetylamino-3'-phenylbutanoyloxy)-9,10-epoxy-9-methyl-(2E,4Z,6E)-2,4,6-decatrienoic acid (**1**) by chemical, spectral, and X-ray crystallographic studies.[1,2] The structure of AK-toxin II (**2**), on the other hand, was assigned to be 3'-demethyl derivative of AK-toxin I (**1**) by comparing the spectral data with those of **1**,[1,2] and this recently was confirmed by the synthesis of **2**[3] and its methyl ester.[4]



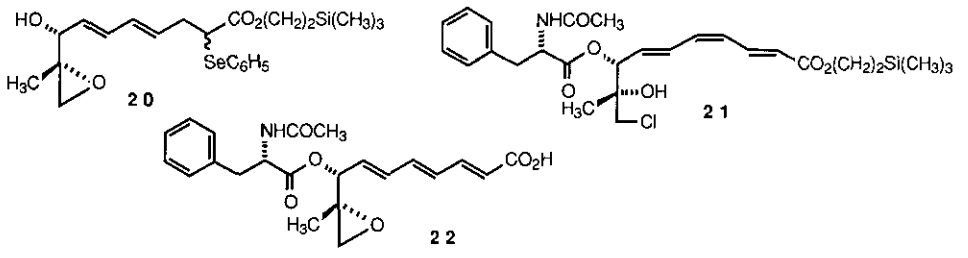
1 R = CH_3 AK-toxin I
2 R = H AK-toxin II

We now wish to describe the total synthesis of AK-toxin II (**2**) starting from D-fructose. The γ-lactone **3** was available on a large scale from D-fructose by the procedure reported.[5] Reduction of **3** with lithium aluminum hydride in ether/tetrahydrofuran (THF) (1:1) at room temperature afforded the triol **4** in 80% yield. Oxidative cleavage of **4** using 1.2 equiv. of sodium periodate in methanol/water (1:1) at 0°C afforded the hemiacetal **5** (72% yield) which was treated with methyl (triphenylphosphoranylidene)acetate in benzene at 80°C to give quantitatively an E/Z mixture (1.8:1, nmr analysis) of the unsaturated ester **6**. Deprotection of **6** (not separated) with 80% aqueous acetic acid at 90°C afforded the triol **7** which was treated with acetone in the presence of trace sulfuric acid to produce the ester **8** as a major product together with the lactone **9** as a minor product (ratio 2:1, total yield 77% overall from **5**). The ester **8** was converted into the aldehyde **10** in 70% overall yield [(1) TMSCl, $(i\text{-}Pr)_2EtN/CH_2Cl_2$, r.t.; (2) DIBAL/toluene, -78°C; (3) MnO_2/ether, r.t.]. Chain extension of **10** to form the diene ester **11** was effected in 84% yield by reaction with the Wittig reagent


D-fructose
3
4
5
6
7
8
9
10
11 R1 = C2H5
12 R2 = (CH2)2Si(CH3)3
13
14 R1 = Si(CH3)3, R2 = H
15 R1 = Si(CH3)3, R2 = SeC6H5
16 R = Si(CH3)3
17 R = H
18 R = NPS
19 R = COCH3
NPS =
2

prepared from (3-ethoxycarbonylpropyl)triphenylphosphonium bromide[6] (1.2 equiv.) and potassium t-butoxide (1.2 equiv.) in THF at -78°C. Product **11** was found quite pure and no contamination of 4E isomer was observed in its nmr spectrum. In order to facilitate the final removal of the protecting group of carboxylic acid affording AK-toxin II, the ethyl ester **11** was converted into the corresponding trimethylsilylethyl ester **12** via a three step sequence in 63% overall yield [(1) NaOH/EtOH, r.t.; (2) TMSCl, $(i\text{-}Pr)_2EtN/CH_2Cl_2$; (3) $(CH_3)_3Si(CH_2)_2OH$, DCC, DMAP/CH_2Cl_2, r.t.]. Hydrolysis of **12** was achieved using 70% aqueous acetic acid at 70°C, and the resultant triol was then mesylated with 1.3 equiv. of methanesulfonyl chloride and diisopropylethylamine in dichloromethane at -20°C to give the desired monomesylate **13** in 78% overall yield from **12**. The mesylate **13** was cyclized to the epoxide (t-BuOK/THF, 0°C), which was then silylated [TMSCl, $(i\text{-}Pr)_2EtN/CH_2Cl_2$, 0°C] to give **14** in 66% overall yield from **13**. The lithium enolate of **14**, prepared using lithium diisopropylamide in THF at -78°C, reacted with diphenyl diselenide to give the diastereomeric mixture of the phenylseleno ester **15** in 67% yield. Unfortunately, acid-induced deprotection (20% AcOH in H_2O, 50°C) of silyl ether group of **15** afforded the epimerized 4E isomer **20** almost quantitatively. Even under basic conditions ($n\text{-}Bu_4N^+F^-$/THF, -30°C or 1N NaOH/EtOH,0°C), a small amount of contamination of 4E isomer was observed in nmr spectra of the products. We decided, therefore, to form $C_{2,3}$ double bond prior to C_8-O deprotection and acylation. Oxidative elimination of phenylseleno group of **15** was performed with 30% hydrogen peroxide in biphasic mixture of dichloromethane and water (1:1) at 0°C to give the triene **16** in 93% yield. The silyl ether protecting group in **16** was removed by 1.1 equiv. of tetrabutylammonium fluoride in THF at -30°C to give **17** in quantitative yield.

At this stage we were ready to attach the phenylalanine side chain. To avoid racemization of the amino acid[7] during esterification, we chose 2-nitrophenylsulfenylphenylalanine (NPS-Phe-OH)[8] as a reagent. Thus, NPS-Phe-OH was reacted with **17** in the presence of dicyclohexylcarbodiimide (1.05 equiv.) and dimethylaminopyridine (0.1 equiv.) in ethyl acetate to give the ester **18** in 93% yield. Removal of NPS group was achieved using 2 equiv. of HCl in ether at 0°C, and the resulting amine was then acetylated *in situ* by the addition of acetic anhydride and pyridine. The only product of this reaction was the chlorohydrin **21** (81% yield), which could be cyclized again by 1 equiv. of potassium t-butoxide in THF to afford the epoxide **19**



in 79% yield. Although the precise mechanism of this regioselective chlorohydrin formation is not clear at present, a mechanism which involves participation of the amino or sulfenylamino group followed by chlorination resulting in the chlorohydrin seems most probable.

Finally, fluoride-induced deprotection (n-$Bu_4N^+F^-$/THF, 20°C) of **19** afforded the carboxylic acid **2** in 46% yield, mp 155-156°C, decomp (lit.[2] mp 163°C, decomp), $[\alpha]_D^{20}$+133.3°(c=0.10, MeOH) [lit[2] $[\alpha]_D^{23}$ +125°(c=0.132, MeOH)], which was found to be identical (uv, ms, ^1H nmr) with AK-toxin II. The 4E isomer (**22**) of AK-toxin II was obtained from **20** via the six step sequence in 17% overall yield [(1) NPS-Phe-OH, $ClCO_2$-i-Bu,NEt_3,DMAP; (2) HCl/ether; (3) Ac_2O/pyridine; (4) t-BuOK/THF; (5) $NaIO_4$/MeOH/H_2O; (6)n-$Bu_4N^+F^-$/THF], mp 213-214°C, decomp., $[\alpha]_D^{20}$+30.2°(c=0.33, MeOH).[9]

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9. Selected data; **8:** ir($CHCl_3$): 1720cm^{-1}; ^1H nmr(200MHz, $CDCl_3$): δ 1.31 (3H, s), 1.44 (6H, s), 2.55 (1H, br, OH), 3.67 (1H, d, J=8.8), 3.76 (3H, s), 4.07 (1H, d, J=8.8), 4.29 (1H, dd, J=2.0, 4.2), 6.21 (1H, dd, J=2.0, 15.8), and 7.01 (1H, dd, J=4.2, 15.8). **9:** ir($CHCl_3$):1760cm^{-1}; ^1H nmr(200MHz, $CDCl_3$): δ 1.14,

1.41, 1.48 (3X3H, s), 3.82 (1H, d, J=9.4), 4.96 (1H, t, J=1.7), 6.24 (1H, dd, J=1.7, 5.9) and 7.57 (1H, dd, J=1.7, 5.9). **11:** ir($CHCl_3$): 1737 and 1253cm^{-1}; ^1H nmr(200MHz, $CDCl_3$): δ 0.13 (9H, s), 1.19, 1.39, 1.41 (3X3H, s), 1.25 (3H, t, J=7.1), 2.38~2.53 (4H, m), 3.66 (1H, d, J=8.7), 4.03 (1H, d, J=8.7), 4.12 (1H, d, J=5.6), 4.13 (2H, q, J=7.1), 5.38 (1H, m), 5.76 (1H, dd, J=5.6, 15.1), 6.05 (1H, t, J=11.0), and 6.50 (1H, dd, J=11.0, 15.1). **17:** ir($CHCl_3$): 1710, 1251, and 837cm^{-1}; ^1H nmr(200MHz, $CDCl_3$): δ 0.07 (9H, s), 1.04 (2H, m), 1.38 (3H, s), 2.37 (1H, br, OH), 2.64 (1H, d, J=4.6), 2.93 (1H, d, J=4.6), 4.26 (1H, d, J=6.6), 4.27 (2H, m), 5.84 (1H, dd, J=6.6, 15.1), 5.91 (1H, d, J=15.3), 6.13 (1H, t, J=11.2), 6.32 (1H, t, J=11.2), 6.96 (1H, dd, J=11.2, 15.1), and 7.75 (1H, dd, J=11.2, 15.3). **19:** ir($CHCl_3$): 3430, 1740, 1698, and 1677cm^{-1}; ^1H nmr(200MHz, $CDCl_3$): δ 0.06 (9H, s), 1.04 (2H, m), 1.31, 2.01 (2X3H, s), 2.61 (1H, d, J=4.8), 2.74 (1H, d, J=4.8), 3.12 (2H, d, J=6.1), 4.26 (2H, m), 4.91 (1H, dt, J=6.1, 7.5), 5.27 (1H, d, J=7.8), 5.68 (1H, dd, J=7.8, 15.1), 5.93 (1H, d, J=7.5, NH), 5.94 (1H, d, J=15.1), 6.19 (1H, t, J=11.0), 6.28 (1H, t, J=10.8), 6.84 (1H, dd, J=10.8, 15.1), 7.06~7.26 (5H, m), and 7.68 (1H, dd, J=11.0, 15.1). **22:** ir($CHCl_3$): 3310, 1743, 1686, 1620, and 1543cm^{-1}; ^1H nmr(400MHz, CD_3OD): δ 1.29, (3H, s), 1.93 (3H, s), 2.60 (1H, d, J=4.9), 2.73 (1H, d, J=4.9), 2.99 (2H, dd, J=8.2, 13.7), 3.10 (1H, dd, J=6.7, 13.7) 4.66 (1H, dd, J=6.7, 8.2), 5.18 (1H, d, J=7.0), 5.72 (1H, dd, J=7.0, 15.3), 5.94 (1H, d, J=15.3), 6.31 (1H, dd, J=10.7, 15.3), 6.44 (1H, dd, J=11.0, 15.0), 6.59 (1H, dd, J=10.7, 15.0), 7.20-7.29 (5H, m), and 7.31 (1H, dd, J=11.0, 15.3).

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