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Total synthesis of AAL-toxin TA_1

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Abstract

Two alternative synthetic routes of the left-half segment **5** have been developed. Efficient condensation between the left and right segments followed by Pd-catalyzed deoxygenation and further elaboration achieved the first total synthesis of AAL-toxin TA_1. This allowed us to synthesize various AAL-toxin analogs which would be useful for investigating SAR studies of AAL-toxins.

Keywords: toxins; condensations.

AAL-toxins TA_1 **1** and TA_2 **2** were isolated as host-specific toxins from *Alternaria alternata* f. sp. *lycopersici*, a causal fungus of tomato stem canker.[1] These toxins reproduce similar symptoms to that of the disease for susceptible genotypes of tomato leaf in concentrations less than 10 ng/ml.[2] Recently, their congeners have been isolated from the same fungus.[3] The relative and absolute configuration of AAL-toxins were elucidated by us[4] and Kishi's group[5] with degradation and synthesis of possible partial structures. AAL-toxins and structurally related analogs fumonisins **3**, **4**[6] have been found to be a tumor promoter[7] and an inhibitor of sphingolipid biosynthesis.[8] AAL-toxins are first compounds which caused apoptosis in both mammalian and plant cell.[9] In order to find a target molecule of AAL-toxins in susceptible tomato cells and to study structure–activity relationships (SAR) of these toxins, we initiated a synthetic study of AAL-toxins.

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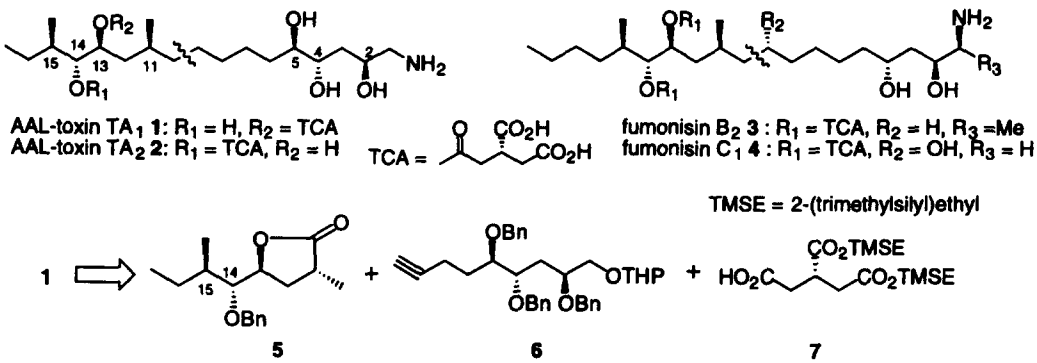
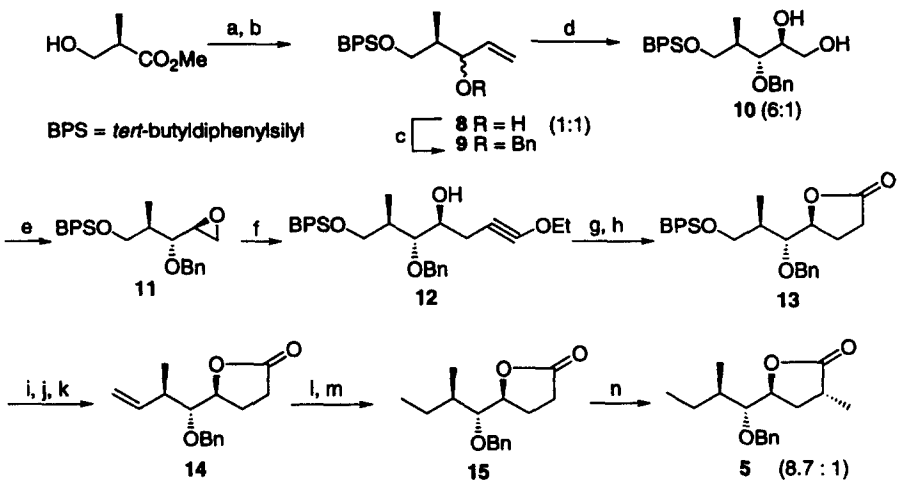


Thus, AAL-toxin TA_1 **1** is retrosynthetically divided into three segments, left and right segments, **5** and **6**, and tricaballylic acid segment **7**. Recently, we reported the efficient syntheses of synthetically equivalent segments.[10] Occurrence of various deoxygenated analogs of **1** and **2** provided SAR information of the right half while none of the analogs concerning the left half has been isolated. In order to examine SAR on the left half, development of the efficient flexible route which can be applied for the synthesis of AAL-toxins and fumonisins is required. Herein, we disclose alternative syntheses of the segment **5** and the first total synthesis of AAL-toxin TA_1 **1** via efficient couplings of the segments **5**, **6** and **7**.

The synthesis of the left-half segment **5** was initiated from methyl 3-hydroxy-2-methylpropionate (Scheme 1). After silylation, treatment with DIBAH gave the corresponding aldehyde which was then reacted with vinyl magnesium bromide in one-pot to afford alcohol **8** in 77% overall yield. Since a kinetic resolution[11] of secondary alcohol **8** was sluggish, we examined separation of diastereomers. Benzylation product **9** was successfully separated by careful SiO_2 column chromatography. Oxidation of the desired anti-isomer of **9** with OsO_4 proceeded stereoselectively to give diol **10** as a 6:1 separable mixture. A major isomer was further transformed to epoxide **11** via Sharpless protocol[12] in 77% yield. Treatment with lithium acetylide prepared from ethyl ethynyl ether in the presence of $BF_3 \cdot Et_2O$[13] afforded adduct **12** which was converted into lactone **13** under sequential hydrolytic conditions in 59% overall yield. Deprotection of silyl group followed by Swern oxidation[14] and Wittig reaction furnished olefin **14**.[15] Hydrogenation and re-benzylation gave **15** which was methylated stereoselectively to afford the left segment **5** as an 8.7:1 separable mixture.

In order to study SAR of **1**, rapid access to late intermediate **5** was next explored (Fig. 1). Aldehyde **16**[16] which is readily prepared from L-glutamate was reacted with various crotylboration reagents[17] as shown in Fig. 1. Although the diastereoselectivity of a desired adduct **17a** was moderate,[18] the reactions proceeded smoothly to give all possible diastereomers **17a–17d** in good yields. Hydrogenation and benzylation of a mixture of **17a** and **17b** provided the common intermediate **15** and its diastereomer as a separable mixture.

All attempts for condensation between the left and the right segments via Wittig or Julia coupling resulted in poor yields. Thus, condensation of lactone **5** with acetylene **6**[19] was conducted (Scheme 2). Treatment of **5** with acetylide prepared from **6** proceeded smoothly to give adduct **18** in excellent yield. Deoxygenation of C-10 carbonyl was achieved by the following three-step procedure. Luche reduction[20] of **18** followed by formylation gave formate **19**. Palladium catalyzed deoxygenation[21] of **19** proceeded with excellent efficiency to give **20**. Sequential deprotection of acyl and THP groups afforded diol **21** which was regioselectively converted to azide **22** by Mitsunobu conditions[22] in 69% yield. Acylation of **22** with the tricarballylic acid moiety **7** by the Yamaguchi method[23] provided **23** in which the TMSE group was removed with TBAF to afford diacid **24**. Finally, reduction of azide and triple bond and hydrogenolysis of all benzyl groups were achieved under the conditions described by Shi et al.[24] to give



Scheme 1. (a) BPSCl, Im, DMF, quant.; (b) DIBAH, Et_2O, –78°C then CH_2=CHMgBr; 77%; (c) NaH, BnBr, *n*-Bu_4NI, THF, 91%; chromatographic separation; (d) OsO_4, NMO, acetone:H_2O (8:1), 91%; (e) $MeC(OMe)_3$, cat. PPTS, CH_2Cl_2; AcBr, CH_2Cl_2; K_2CO_3, MeOH, 77%; (f) ethyl ethynyl ether, *n*-BuLi, $BF_3 \cdot Et_2O$, THF, –78°C; (g) $HgCl_2$, EtOH; (h) K_2CO_3, MeOH, then 3 M HCl, 59% (3 steps); (i) TBAF, THF, 80%; (j) Swern oxid.; (k) Ph_3PCH_3Br, *n*-BuLi, THF, 19% (2 steps, recovered aldehyde 70%); (l) H_2, Pd-C, EtOAc; (m) CCl_3C(=NH)OBn, TfOH, CH_2Cl_2:cyclohexane (1:1), 57% (2 steps); (n) LiHMDS, CH_3I, THF, –78°C, 68%

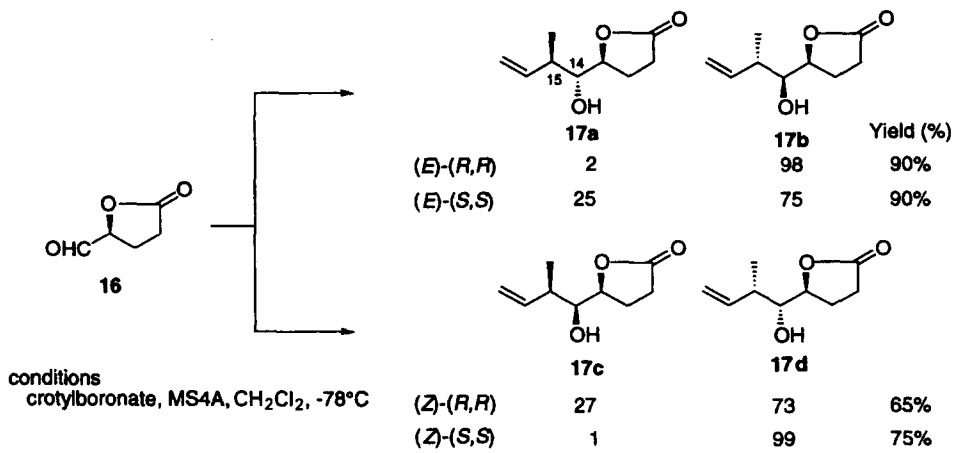


Figure 1.

AAL-toxin TA_1 which is identical to a natural product in all respects ($[\alpha]_{577}^{28}$ –20 (c 0.25, H_2O); lit.[4] $[\alpha]_{577}^{22}$ –23 (c 1.9, H_2O)).

In conclusion, we developed two alternative routes of the left-half segment **5** and achieved the first total synthesis of AAL-toxin TA_1. This allowed us to synthesize various AAL-toxin analogs which would be useful for investigating SAR studies of AAL-toxin.

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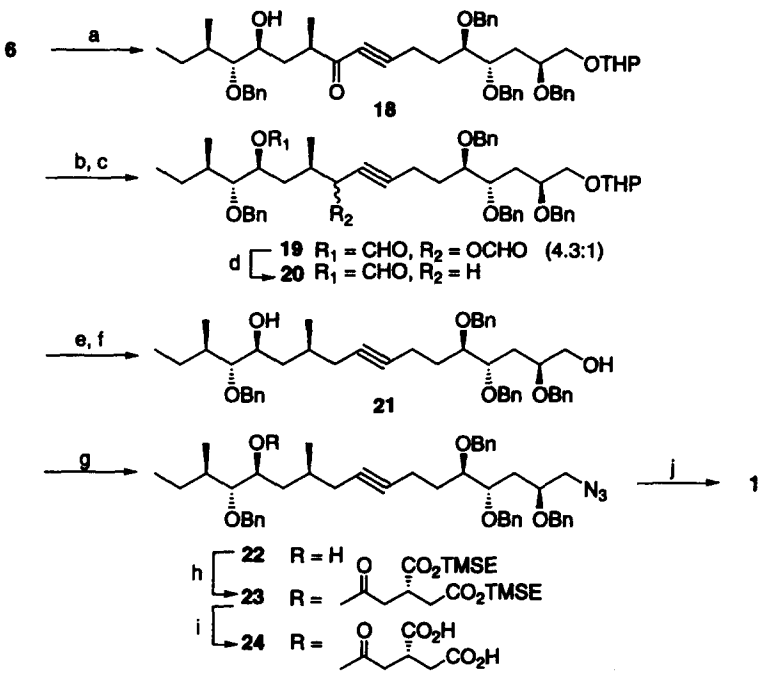

Scheme 2. (a) *n*-BuLi, ether, –20°C; **5**, 72%; (b) $NaBH_4$, $CeCl_3$, MeOH, 85%; (c) Ac_2O, HCO_2H, Py, 97%; (d) $Pd(OAc)_2$, *n*-Bu_3P, THF, 84%; (e) $LiAlH_4$, THF; (f) PPTS, EtOH, 89% (2 steps); (g) HN_3, Ph_3P, DEAD, toluene, 69%; (h) 2,4-$NO_2C_6H_4COCl$, **7**, Et_3N, toluene then **22**, DMAP, 71%; (i) TBAF, THF; (j) H_2, Pd-C, *t*-BuOH-THF-1 M HCl (3:1:0.04), 76% (2 steps)

of authentic AAL-toxin. This work was supported by a Grant-in-Aids from the Ministry of Education, Science, and Culture of Japan, and partly by Shourai Foundation for Science and Technology.

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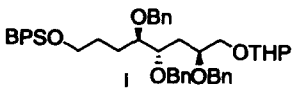

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