



Synthetic Study of AAL-toxins: Efficient Construction of Two Vicinal Diol Moieties by Asymmetric Dihydroxylation

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Abstract: Asymmetric dihydroxylation has been applied to syntheses of two vicinal *anti*-diol moieties in key intermediates of AAL-toxins. The strategy allowed efficient construction of left- and right segments of AAL-toxin main chain. Copyright © 1996 Elsevier Science Ltd

AAL-toxins TA₁ **1** and TA₂ **2** were isolated as host-specific toxins from *Alternaria alternata* f. sp. *lycopersici*, a causal fungus of tomato stem canker.¹ Recently, the structurally related analogues fumonisins have been found to be a tumor promoter² and an inhibitor of sphingolipid biosynthesis.³ Both class of compounds exhibited similar biological activities in both mammalian cell and plant cell.⁴ Considerable efforts for elucidating relative and absolute configuration of both toxin families made by us⁵ and the others^{6,7} have allowed to establish their structures as shown in Fig. 1. In order to find a target molecule of AAL-toxins in susceptible tomato cell and to study structure-activity relationship of these toxins, we initiated a synthetic study of AAL-toxins.

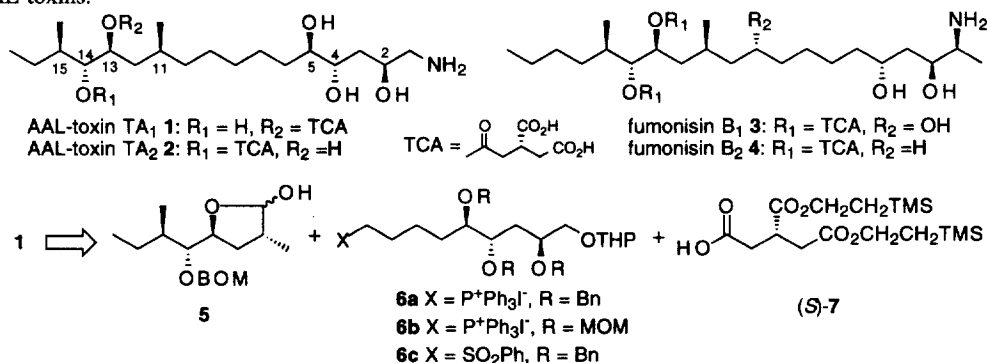
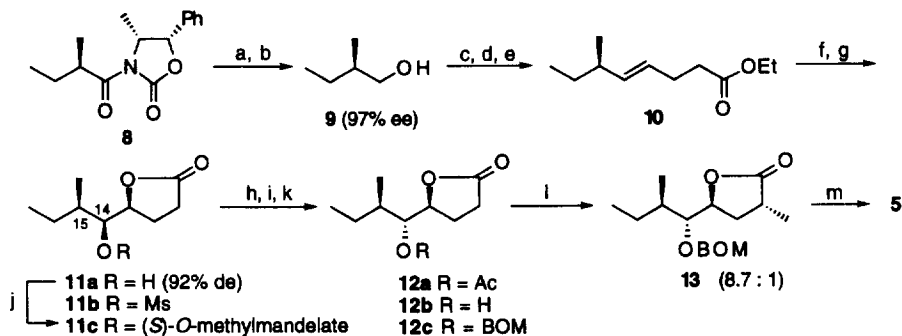


Fig. 1

Among eight chiral centers in AAL-toxin molecule, four of them are originated from two vicinal diol moieties. Introducing such functionality, we applied asymmetric dihydroxylation (AD)⁸ which significantly simplified our synthetic routes. Thus, AAL-toxin TA₁ **1** is retrosynthetically divided into three segments, left- and right segments, **5** and **6a-6c**, and tricarballylic acid segment (S)-**7**. Herein, we disclose efficient syntheses of those segments.

The synthesis of the left-half segment **5** began with Evans alkylation product **8**⁹ whose diastereomer is separable by SiO₂ chromatography (Scheme 1). In preliminary studies, we noticed that separation of diastereomers concerning C-14 and C-15 was rather difficult.^{5c} Thus, we gave up direct introduction of *anti*-

diol using less enantioselective AD of *Z*-olefin,^{8b} and chose the strategy using AD of *E*-olefin **10** and subsequent inversion of the stereochemistry introduced. Oxazolidinone **8** was converted to alcohol **9** by a standard procedure.¹⁰ Conversion of **9** into *E*-olefin **10** was accomplished in 53% yield by Swern oxidation and addition of vinyl magnesium bromide followed by orthoester-Claisen rearrangement.



Scheme 1 (a) 30% H₂O₂, LiOH; (b) LiAlH₄, Et₂O, 77% (2 steps); (c) Swern oxid.; (d) CH₂=CHMgBr, THF, -78°C; (e) CH₃C(OEt)₃, CH₃CH₂CO₂H, reflux, 53% (3 steps); (f) AD-mix- α , 75%; (g) MsCl, Et₃N, CH₂Cl₂; (h) CsOAc, 18-crown-6, C₆H₆, reflux; (i) KOH, EtOH-H₂O, 70% (3 steps); (j) (*S*)-*O*-methylmandelic acid, DMAP, DCC, CH₂Cl₂; (k) BOMCl, *i*-Pr₂NEt, CH₂Cl₂; (l) LiHMDS, CH₃I, THF, -78°C, 60% (2 steps); (m) DIBAH, Et₂O, -78°C, 96%.

Asymmetric dihydroxylation of **10** with AD-mix- α and concomitant lactonization furnished lactone **11a** whose diastereomer was carefully separated by SiO₂ chromatography. Diastereoselectivity in this reaction was determined as 92% de by HPLC analysis of the corresponding mandelate ester **11c**. Mitsunobu reaction¹¹ of the resultant sterically hindered secondary alcohol **11a** under various conditions gave dehydration product predominantly. Inversion of C-14 stereochemistry in **11a** was achieved under Ikegami's procedure.¹² Mesylation and subsequent treatment of **11b** with CsOAc in the presence of 18-crown-6 furnished **12a** in good overall yield. After hydrolysis and protection with BOM group, the methylation of the resultant **12c** with

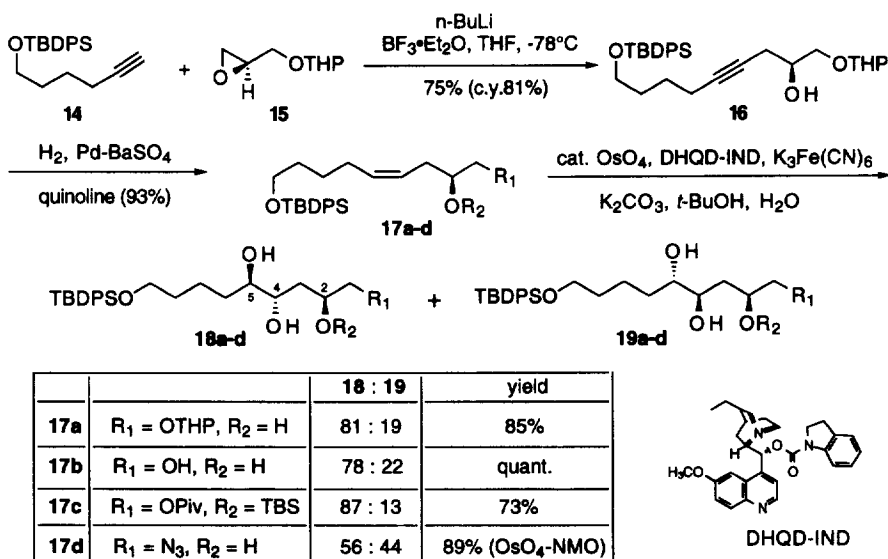
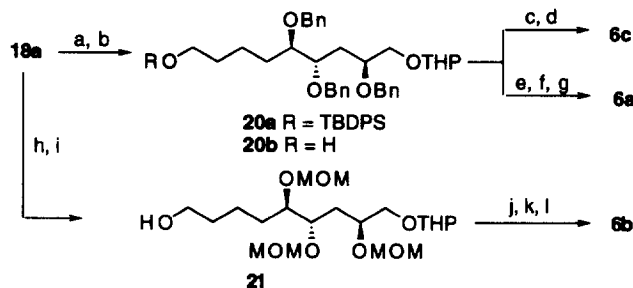


Fig. 2

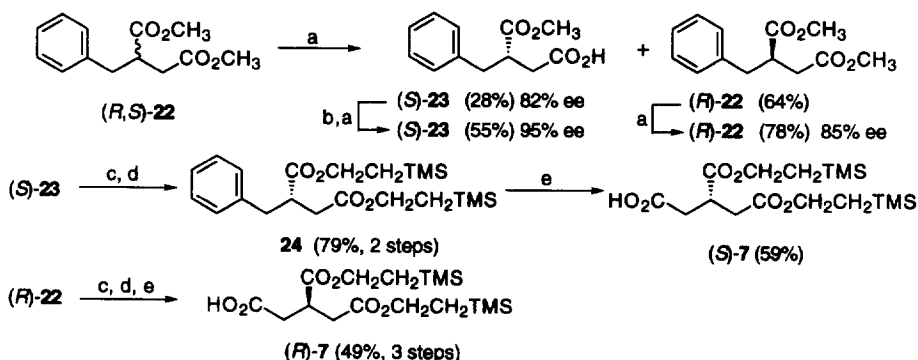
LiHMDS and CH_3I proceeded with good diastereoselectivity (8.7:1) to afford 13^{13} which were reduced with DIBAH to furnish the left-half segment **5**.

The synthetic routes of the right-half segments **6a-6c** were described in Fig. 2 and Scheme 2. Condensation of lithium acetylide derived from **14** with epoxide **15** prepared from (*R*)-glycidol in the presence of $\text{BF}_3 \cdot \text{OEt}_2^{14}$ gave adduct **16** in 75% yield with 7% of starting material. After partial hydrogenation, the resultant *Z*-olefin **17a** was converted to its analogues **17b-17d**. For these derivatives, AD using ligand DHQD-IND¹⁵ was examined. In all cases, desired 2,4-*anti*-diols **18a-18d**¹⁶ were obtained as major products which were able to be separated by SiO_2 chromatography. Although a little increase of the diastereoselectivity was observed in reaction of **17c**, bulky protective groups nor C-2 hydroxy group did not play an important role in AD of the *Z*-olefins.



Scheme 2 (a) NaH, BnBr, *n*-Bu₄NI, THF, reflux, 81%; (b) TBAF, THF, 89%; (c) $(\text{PhS})_2$, *n*-Bu₃P, CH_2Cl_2 ; (d) mCPBA, CH_2Cl_2 , 89% (2 steps); (e) TsCl, Et₃N, CH_2Cl_2 ; (f) NaI, acetone, 83% (2 steps); (g) Ph_3P , *i*-Pr₂NEt, CH_3CN , reflux, 45%; (h) MOMCl, *i*-Pr₂NEt, CH_2Cl_2 ; (i) TBAF, THF, 83% (2 steps); (j) TsCl, Et₃N, CH_2Cl_2 ; (k) NaI, acetone, 76% (2 steps); (l) Ph_3P , *i*-Pr₂NEt, CH_3CN , reflux, 76%.

Major AD product **18a** was transformed into several coupling units as shown in Scheme 2. Complete benzylation of **18a** yielded tribenzyl ether **20a** which was hydrolyzed to alcohol **20b**. Sulfination and followed oxidation with mCPBA afforded sulfone **6c**. Alcohol **20b** was also converted to phosphonium salt **6a** by a standard procedure. However, transformation of the corresponding iodide to **6a** was sluggish (less than 45%) and changes of reaction conditions (solvents, concentration, addition of amine) did not improve the yield significantly. Therefore, MOM protected phosphonium salt **6b** was prepared from **18a** by nearly identical procedure. In this case, the yield (76%) of the conversion from the iodide to **6b** was acceptable.



Scheme 3 (a) PPL, 0.1M KH_2PO_4 (pH 7.2); (b) CH_2N_2 ; (c) 1M NaOH, MeOH; (d) $\text{TMSCH}_2\text{CH}_2\text{OH}$, EDC, Et₃N, DMAP, CH_2Cl_2 ; (e) RuCl_2 , NaIO₄, CCl_4 - CH_3CN - H_2O (2:2:3).

In the synthesis of tricarballic acid segment, we applied lipase-catalyzed kinetic resolution of 2-benzylsuccinate **22**.¹⁷ Racemic diester **22** was hydrolyzed by PPL. After 28% conversion, (*S*)-**23** was

obtained in 82% ee.¹⁸ Methylation with diazomethane and second PPL-hydrolysis of the resultant monoester afforded (*S*)-**23** in 95% ee (55% conversion). From the diester recovered in the first hydrolysis, (*R*)-diester **22** was also obtained in 84% ee in 22% conversion by resubjection to PPL-hydrolysis. Hydrolysis of (*S*)-diester followed by protection with trimethylsilylethyl group gave suitable protected diester **24**. RuO₄-catalyzed oxidation of **24** afforded the tricarballic acid segment (*S*)-**7**. Similar conversion of (*R*)-**22** gave (*R*)-**7**.

In conclusion, we synthesized three key intermediates **5** (16% overall yield from **9**), **6b** (25% from **15**) and (*S*)-**7** (7% from (*R,S*)-**22**) of our AAL-toxin synthesis in efficient manners. The synthetic routes shown above should be applied to synthesis of fumonisins and also various types of AAL-toxin and fumonisin analogues. Using these segments, we are currently examining their coupling conditions.

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