Pergamon

Tetrahedron Letters, Vol. 37, No. 34, pp. 6169-6172, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01339-1

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

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Key Words: AAL-toxin; host-specific toxin; *Alternaria alternata*; asymmetric dihydroxylation

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 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] Recently, the structurally related analogues fumonisins have been found to be a tumor promoter [2] 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 us[5] 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.

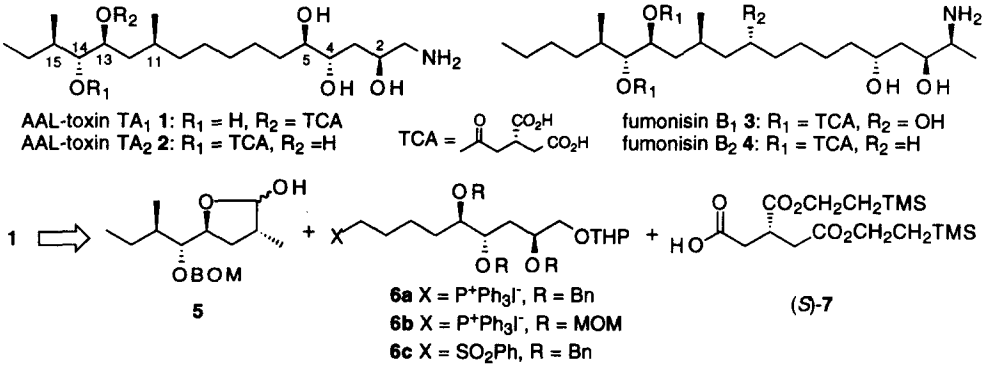
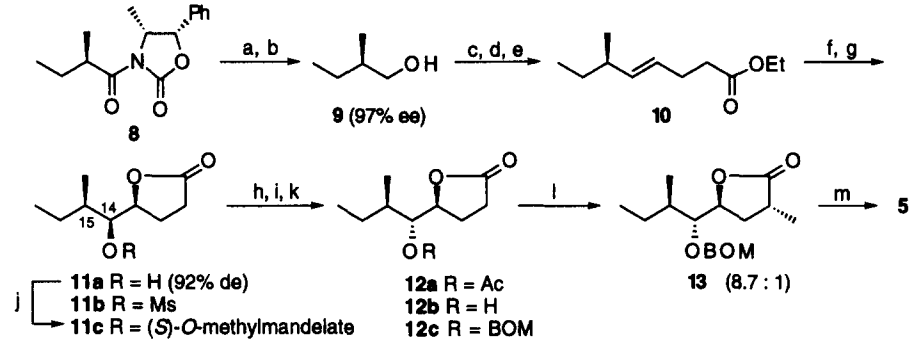


Fig. 1

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 TA_1 **1** is retrosynthetically divided into three segments, left- and right segments, **5** and **6a-6c**, and tricaballylic acid segment (*S*)-**7**. Herein, we disclose efficient syntheses of those segments.

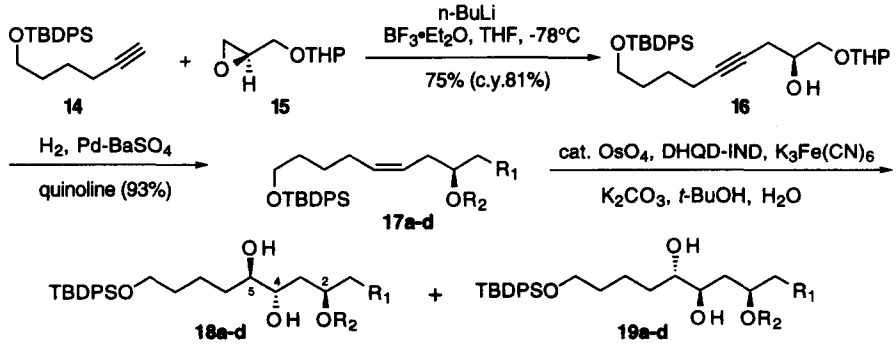
The synthesis of the left-half segment **5** began with Evans alkylation product **8**[9] whose diastereomer is separable by SiO_2 chromatography (Scheme 1). In preliminary studies, we noticed that separation of diastereomers concerning C-14 and C-15 was rather difficult.[5c] Thus, we gave up direct 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.

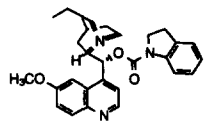


Scheme 1 (a) 30% H_2O_2, LiOH; (b) $LiAlH_4$, Et_2O, 77% (2 steps); (c) Swern oxid.; (d) CH_2=CHMgBr, THF, -78°C; (e) $CH_3C(OEt)_3$, $CH_3CH_2CO_2H$, reflux, 53% (3 steps); (f) AD-mix-α, 75 %; (g) MsCl, Et_3N, CH_2Cl_2; (h) CsOAc, 18-crown-6, C_6H_6, reflux; (i) KOH, EtOH-H_2O, 70% (3 steps); (j) (*S*)-*O*-methylmandelic acid, DMAP, DCC, CH_2Cl_2; (k) BOMCl, i-Pr_2NEt, CH_2Cl_2; (l) LiHMDS, CH_3I, THF, -78°C, 60 % (2 steps); (m) DIBAH, Et_2O, -78°C, 96%.

Asymmetric dihydroxylation of **10** with AD-mix-α and concomitant lactonization furnished lactone **11a** whose diastereomer was carefully separated by SiO_2 chromatography. Diastereoselectivity in this reaction was determined as 92% de by HPLC analysis of the corresponding mandelate ester **11c**. Mitsunobu reaction[11] 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



		18 : 19	yield
17a	R_1 = OTHP, R_2 = H	81 : 19	85%
17b	R_1 = OH, R_2 = H	78 : 22	quant.
17c	R_1 = OPiv, R_2 = TBS	87 : 13	73%
17d	R_1 = N_3, R_2 = H	56 : 44	89% (OsO_4-NMO)

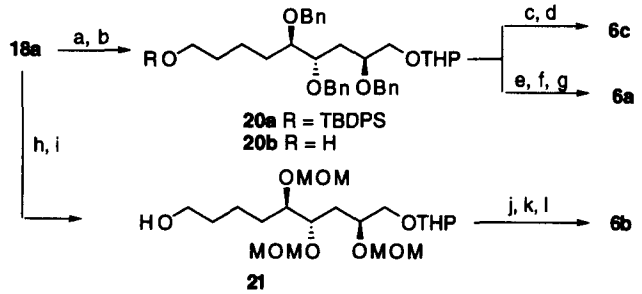


DHQD-IND

Fig. 2

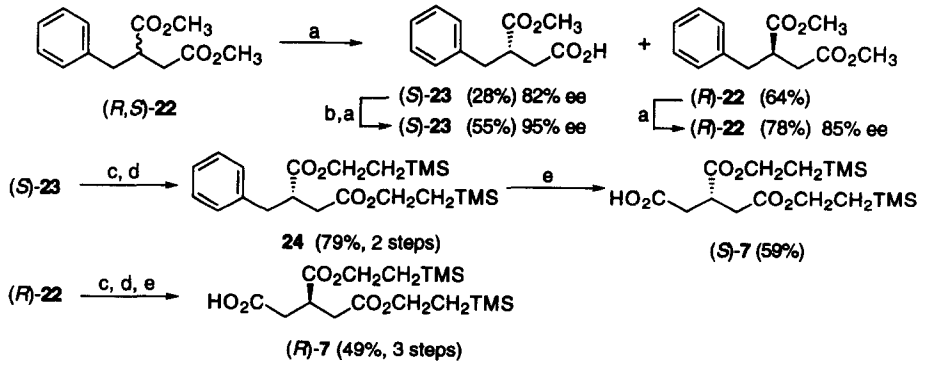
LiHMDS and CH_3I proceeded with good diastereoselectivity (8.7:1) to afford **13**[13] which were reduced with DIBAH to furnish the left-half segment **5**.

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 $BF_3{\cdot}OEt_2$[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-IND[15] 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-Bu_4NI, THF, reflux, 81%; (b) TBAF, THF, 89%; (c) $(PhS)_2$, n-Bu_3P, CH_2Cl_2; (d) mCPBA, CH_2Cl_2, 89% (2 steps); (e) TsCl, Et_3N, CH_2Cl_2; (f) NaI, acetone, 83% (2 steps); (g) Ph_3P, i-Pr_2NEt, CH_3CN, reflux, 45%; (h) MOMCl, i-Pr_2NEt, CH_2Cl_2; (i) TBAF, THF, 83% (2 steps); (j) TsCl, Et_3N, CH_2Cl_2; (k) NaI, acetone, 76% (2 steps); (l) Ph_3P, i-Pr_2NEt, 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) $TMSCH_2CH_2OH$, EDC, Et_3N, DMAP, CH_2Cl_2; (e) $RuCl_2$, $NaIO_4$, CCl_4-CH_3CN-H_2O (2:2:3).

In the synthesis of tricarballylic 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**. RuO_4-catalyzed oxidation of **24** afforded the tricarballylic 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.

We are grateful to Mr. K. Watanabe and Mrs. E. Fukushi in our department for their measurements of MS spectra, and Miss. T. Wakayama for preliminary experiments of tricarballylic segment. This work was supported by a Grant-in-Aids from the Ministry of Education, Science, and Culture of Japan.

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(*Received in Japan* 6 *June* 1996; *revised* 1 *July* 1996; *accepted* 5 *July* 1996)