



Pergamon

Tetrahedron Letters 40 (1999) 6621–6625

TETRAHEDRON
LETTERS

Total synthesis of AAL-toxin TA₁

Hideaki Oikawa,* Daisuke Yamawaki, Takashi Kagawa and Akitami Ichihara

Department of Bioscience and Chemistry, Faculty of Agriculture, Hokkaido University, Sapporo 060, Japan

Received 11 June 1999; revised 28 June 1999; accepted 2 July 1999

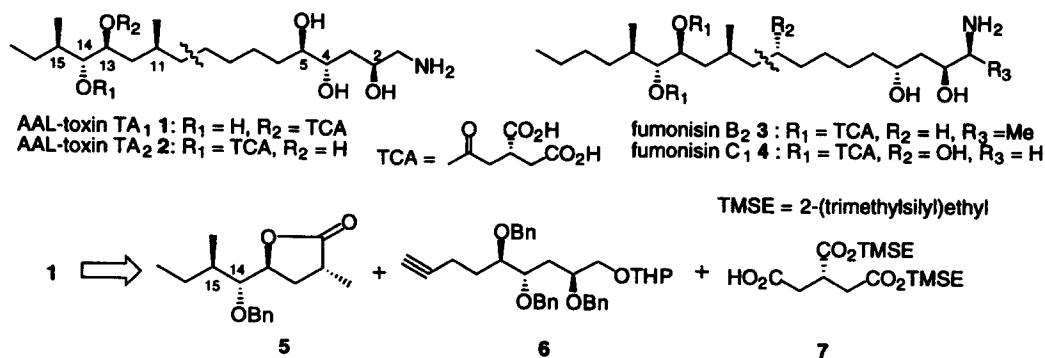
Abstract

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 TA₁. This allowed us to synthesize various AAL-toxin analogs which would be useful for investigating SAR studies of AAL-toxins. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: toxins; condensations.

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 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 us⁴ and Kishi's group⁵ 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 promoter⁷ 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.

* Corresponding author.

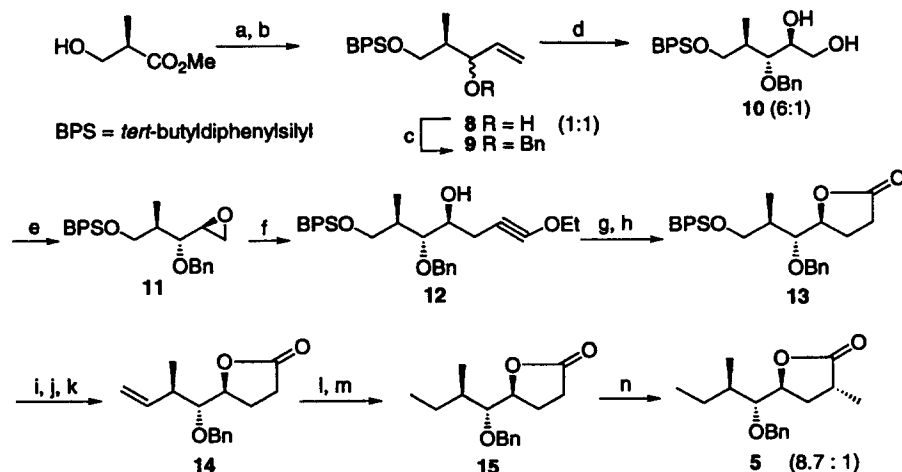


Thus, AAL-toxin TA₁ **1** is retrosynthetically divided into three segments, left and right segments, **5** and **6**, and tricarballylic acid segment **7**. Recently, we reported the efficient syntheses of synthetically equivalent segments.¹⁰ Occurrence of various deoxygenated analogs of **1** and **2** 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 TA₁ **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 resolution¹¹ of secondary alcohol **8** was sluggish, we examined separation of diastereomers. Benzylation product **9** was successfully separated by careful SiO₂ column chromatography. Oxidation of the desired anti-isomer of **9** with OsO₄ proceeded stereoselectively to give diol **10** as a 6:1 separable mixture. A major isomer was further transformed to epoxide **11** via Sharpless protocol¹² in 77% yield. Treatment with lithium acetylide prepared from ethyl ethynyl ether in the presence of BF₃·Et₂O¹³ afforded adduct **12** which was converted into lactone **13** under sequential hydrolytic conditions in 59% overall yield. Deprotection of silyl group followed by Swern oxidation¹⁴ and Wittig reaction furnished olefin **14**.¹⁵ Hydrogenation and re-benylation 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 reagents¹⁷ 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 reduction²⁰ of **18** followed by formylation gave formate **19**. Palladium catalyzed deoxygenation²¹ 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 conditions²² in 69% yield. Acylation of **22** with the tricarballylic acid moiety **7** by the Yamaguchi method²³ 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) BPSO, Im, DMF, quant.; (b) DIBALH, Et₂O, -78°C then CH₂=CHMgBr; 77%; (c) NaH, BnBr, *n*-Bu₄NI, THF, 91%; chromatographic separation; (d) OsO₄, NMO, acetone:H₂O (8:1), 91%; (e) MeC(OMe)₃, cat. PPTS, CH₂Cl₂; AcBr, CH₂Cl₂; K₂CO₃, MeOH, 77%; (f) ethyl ethynyl ether, *n*-BuLi, BF₃·Et₂O, THF, -78°C; (g) HgCl₂, EtOH; (h) K₂CO₃, MeOH, then 3 M HCl, 59% (3 steps); (i) TBAF, THF, 80%; (j) Swern oxid.; (k) Ph₃PCH₂Br, *n*-BuLi, THF, 19% (2 steps, recovered aldehyde 70%); (l) H₂, Pd-C, EtOAc; (m) CCl₃C(=NH)OBn, TfOH, CH₂Cl₂:cyclohexane (1:1), 57% (2 steps); (n) LiHMDS, CH₃I, THF, -78°C, 68%

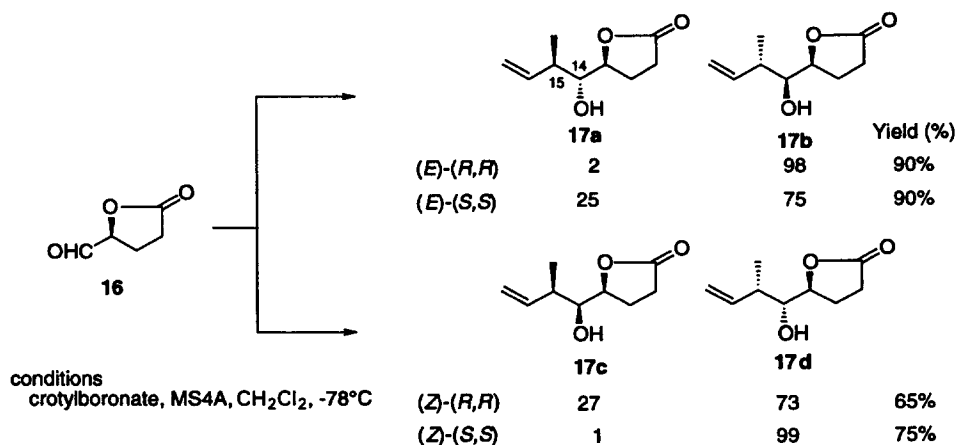


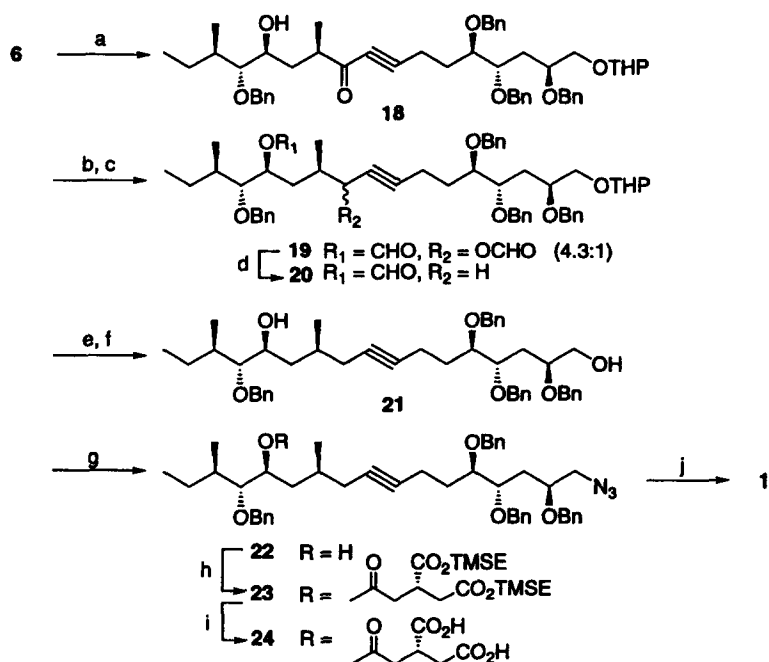
Figure 1.

AAL-toxin TA₁ which is identical to a natural product in all respects ($[\alpha]_{577}^{28} -20$ (c 0.25, H₂O); lit.⁴ $[\alpha]_{577}^{22} -23$ (c 1.9, H₂O)).

In conclusion, we developed two alternative routes of the left-half segment **5** and achieved the first total synthesis of AAL-toxin TA₁. This allowed us to synthesize various AAL-toxin analogs which would be useful for investigating SAR studies of AAL-toxin.

Acknowledgements

We are grateful to Mr. K. Watanabe and Mrs. E. Fukushi in our department for their measurements of MS spectra, and Professor Kohmoto, Faculty of Agriculture, Tottori University for providing a sample



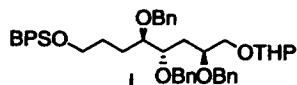
Scheme 2. (a) *n*-BuLi, ether, -20°C ; 5, 72%; (b) NaBH₄, CeCl₃, MeOH, 85%; (c) Ac₂O, HCO₂H, Py, 97%; (d) Pd(OAc)₂, *n*-Bu₃P, THF, 84%; (e) LiAlH₄, THF; (f) PPTS, EtOH, 89% (2 steps); (g) HN₃, Ph₃P, DEAD, toluene, 69%; (h) 2,4-NO₂C₆H₄COCl, 7, Et₃N, toluene then 22, DMAP, 71%; (i) TBAF, THF; (j) H₂, Pd-C, *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.

References

- Bottini, A. T.; Bowen, J. R.; Gilchrist, D. G. *Tetrahedron Lett.* **1981**, *22*, 2723–2726; Bottini, A. T.; Gilchrist, D. G. *Tetrahedron Lett.* **1981**, *22*, 2719–2722.
- Kohmoto, K.; Verma, V. S.; Nishimura, S.; Takagi, M.; Scheffer, R. P. *J. Fac. Agric. Tottori Univ.* **1982**, *17*, 1–8; Siler, D. J.; Gilchrist, D. G. *Physiol. Plant Pathol.* **1983**, *23*, 263–274.
- Caldas, E. D.; Jones, A. D.; Ward, B. L.; Winter, C. K.; Gilchrist, D. G. *J. Agric. Food Chem.* **1994**, *42*, 327–333.
- Oikawa, H.; Matsuda, I.; Ichihara, A.; Kohmoto, K. *Tetrahedron Lett.* **1994**, *35*, 1223–1226; Oikawa, H.; Matsuda, I.; Kagawa, T.; Ichihara, A.; Kohmoto, K. *Tetrahedron* **1994**, *50*, 13347–13368.
- Boyle, C. D.; Harmange, J.-C.; Kishi, Y. *J. Am. Chem. Soc.* **1994**, *116*, 4995–4996; Boyle, C. D.; Kishi, Y. *Tetrahedron Lett.* **1995**, *36*, 5695–5698.
- Gelderblom, W. C. A.; Jaskiewicz, K.; Marasas, W. F. O.; Theil, P. G.; Horak, R. M.; Vleggaar, R.; Kreik, N. P. *J. Appl. Environ. Microbiol.* **1988**, *54*, 1806–1811.
- Gilchrist, D. G.; Ward, B.; Moussatos, V.; Mirocha, C. J. *Mycopathologia* **1992**, *117*, 57–64; Mirocha, C. J.; Gilchrist, D. G.; Shier, W. T.; Abbas, H. K.; Wen, Y.; Vesonder, R. F. *Mycopathologia* **1992**, *117*, 47–56.
- Merrill Jr., A. H.; Wang, E.; Gilchrist, D. G.; Riley, R. T. *Advances in Lipid Research* **1993**, *26*, 215–234.
- Gilchrist, D. G. *Cell Death Differ.* **1997**, *4*, 689–698.
- Oikawa, H.; Kagawa, T.; Kobayashi, T.; Ichihara, A. *Tetrahedron Lett.* **1996**, *37*, 6169–6172.
- Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780.
- Kolb, H. C.; Sharpless, K. B. *Tetrahedron* **1992**, *48*, 10515–10530.
- Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391–394; Eis, M. J.; Wrobel, J. E.; Ganem, B. *J. Am. Chem. Soc.* **1984**, *106*, 3693–3694.

14. Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480–2482.
15. During the Wittig reaction, significant amounts of the β -elimination product were formed. Thus, the reaction was terminated before completion.
16. Doolittle, R. E.; Tumlinson, J. H.; Proveaux, A. T.; Heath, R. R. *J. Chem. Ecol.* **1980**, *6*, 473–485.
17. Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348–6359.
18. Predominance of mismatched pairs in crotylboration with Roush's reagent have been reported. See: (a) Niel, G.; Roux, F.; Maisonnasse, Y.; Maugras, I.; Poncet, J.; Jouin, P. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1275–1280; (b) Zheng, W.; DeMattei, J. A.; Wu, J.-P.; Duan, J. J.-W.; Cook, L. R.; Oinuma, H.; Kishi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 7946–7968.
19. The C_1 -shorter homolog **i** was synthesized by the essentially same method reported previously.¹⁰ From the intermediate **i**, the right segment **6** was synthesized in three steps: (i) TBAF, THF, 89%; (ii) CBR_4 , Ph_3P , i - Pr_2NEt , CH_2Cl_2 , 75%; and (iii) n -BuLi, $BF_3 \cdot Et_2O$, THF, $-78^\circ C$, 75%.



20. Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226–2227.
21. Tsuji, J.; Mandai, T. *Synthesis* **1996**, 1–24.
22. Mitsunobu, O. *Synthesis* **1981**, 1–28.
23. Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.
24. Shi, Y.; Peng, L. F.; Kishi, Y. *J. Org. Chem.* **1997**, *62*, 5666–5667.