Tetrahedron Letters, Vol.32, No.38, pp 5141-5142, 1991
Printed in Great Britain

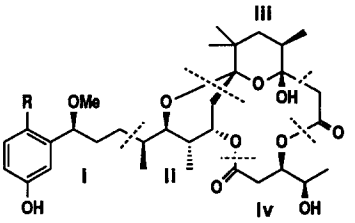
0040-4039/91 $3.00 + .00
Pergamon Press plc

A FORMAL TOTAL SYNTHESIS OF APLYSIATOXIN

Hiroaki Okamura, Satoru Kuroda, Satoru Ikegami, Yoshio Ito, Tsutomu Katsuki,* and Masaru Yamaguchi
Department of Chemistry, Faculty of Science, Kyushu University 33,
Hakozaki, Higashi-ku, Fukuoka 812, Japan

Summary: A total synthesis of aplysiatoxin was achieved formally by construction of Kishi's intermediate **13** which carried all the stereochemistry required for the synthesis of aplysiatoxin, from four fragments described in the preceding communication.

Since the four optically active fragments corresponding to each parts (**i~iv**) in aplysiatoxin (**1**) as shown below, was elaborated by using asymmetric epoxidation and [2,3] Wittig rearrangement as reported in the preceding communication,[1] construction of the four fragments to **1** in a convergent manner was attempted.

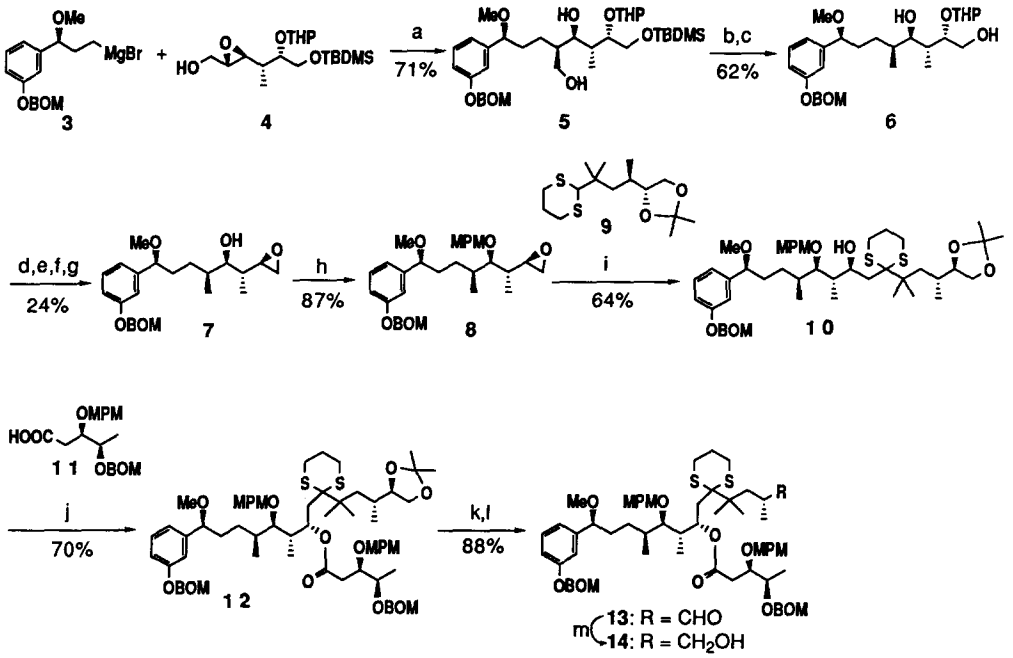


1: R = Br Aplysiatoxin
2: R = H Debromoaplysiatoxin

The synthesis started with the coupling of fragments **3** and **4** which corresponded to **i** and **ii**, respectively, as described in **Scheme 1**. Thus, treatment of epoxy alcohol **4** with Grignard reagent **3** in the presence of CuI provided 1,3-diol **5**[2] and a small amount of undesired stereoisomer.[3] This mixture was used for the next step without separation. The resulting hydroxymethyl group in **5** was converted into methyl group by mesylation and subsequent LAH reduction. In the latter process, the cleavage of the TBDMS ether occurred simultaneously to give 1,4-diol **6**. Conversion of **6** into epoxide **7** was effected by the sequence; i) acetylation of hydroxy groups, ii) acid hydrolysis of THP ether,[4] iii) mesylation of the resulting hydroxy group, and iv) alkaline hydrolysis of acetates accompanying epoxide ring formation. The minor undesired diastereomer produced at the coupling of **3** and **4** (*vide supra*), could be removed by column chromatography (SiO_2) at this stage. Protection of hydroxy group of **7** as a MPM ether[5] gave compound **8**, which set the stage for the coupling with fragment **9** corresponding to **iii**.

Coupling of them was accomplished by treatment of **8** with lithioanion derived from **9**. Condensation of the resulting alcohol **10** and carboxylic acid **11** was accomplished by using Yamaguchi method[6] to give ester **12** which contained all the asymmetric centers to construct **1**. After the acid hydrolysis of the acetonide, treatment of **12** with lead tetraacetate[7] gave aldehyde **13** which was a key intermediate in Kishi's synthesis.[8] For the structure confirmation, **13** was further converted into another Kishi's intermediate **14**. Both **13** and **14** gave identical ^1H NMR spectra in every respects with those of the corresponding authentic samples.

Since **13** has been reported to be convertible to **1** in 7 steps,[8] our accomplishment constitutes a formal total synthesis of optically active aplysiatoxin in an enantiospecific manner.



a) CuI; b) MsCl, Et_3N; c) LAH; d) Ac_2O, DMAP; e) PPTS, MeOH; f) MsCl, DMAP; g) KOH, MeOH; h) MPMCl, NaH; i) **9**, ^{n}BuLi, TMEDA; j) **11**, 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP; k) PPTS, MeOH; l) $Pb(OAc)_4$, AcOK; m) $LiAlH(O^tBu)_3$

Scheme 1

The authors thank Professor Y. Kishi of Harvard University for his kind providing ^1H NMR spectra of intermediates and aplysiatoxins. Financial support from Grand-in-Aid (No 63303003 and 62214010) from the Ministry of Education, Science, and Culture, Japan and Ono pharmaceutical company were also greatly acknowledged.

References and Notes

1) H. Okamura, S. Kuroda, K. Tomita, S. Ikegami, Y. Sugimoto, S. Sakaguchi. T. Katsuki, and M. Yamaguchi, *Tetrahedron Lett.*, the preceding communication.

2) Satisfactory ^1H NMR (90 MHz or 400 MHz) data were obtained for all compounds.

3) The coupling product was consisted of **5** and its diastereomer in a ratio of 9:1 because **4** of 71% ee (reference 1) was coupled with **3** of 96%ee.

4) M. Miyashita, A. Yoshikoshi, and P. A. Grieco, *J. Org. Chem.*, **42**, 3772 (1977).

5) Y. Oikawa, T. Yoshioka, and O.Yonemitsu, *Tetrahedron Lett.*, **23**, 885 (1982).

6) J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, and M., Yamaguchi, *Bull. Chem. Soc. Jpn.*, **52**, 1989 (1979).

7) E. J. Corey, L. O. Weige, A. R. Chamberlin, and B. Lipshutz, *J. Am. Chem. Soc.*, **102**, 1439 (1980).

8) P. Park, C. A. Broka, B. F. Jhonson, and Y. Kishi, *J. Am. Chem. Soc.*, **109**, 6205 (1987).

(Received in Japan 20 May 1991)