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SYNTHESIS OF APLYSIATOXIN: STEREOSELECTIVE SYNTHESIS OF KEY FRAGMENTS

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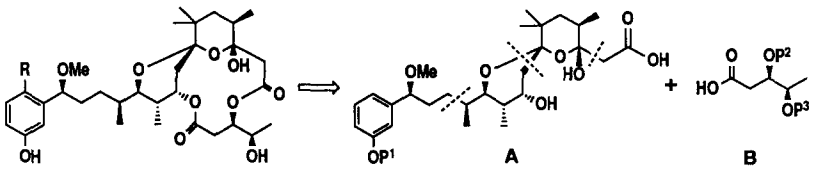
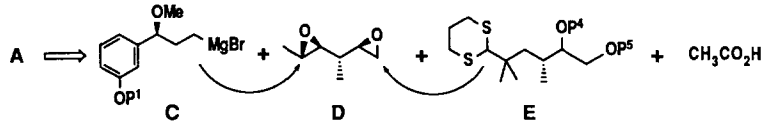
Summary: Stereoselective synthesis of key fragments for the synthesis of aplysiatoxin has been achieved. All the stereogenic carbons contained in fragments **B~E** were elaborated on the basis of [2,3] Wittig rearrangement and titanium-mediated asymmetric epoxidation.

Aplysiatoxin (**1**) and debromoaplysiatoxin (**2**) isolated from the digestive grand of sea hare *Stylocheilus longicauda*, have received much attentions as attractive targets for total synthesis due to their unique molecular architecture together with peculiar biological activities such as strong cancer promotion.[1] Several synthetic approaches to this class of compounds have appeared in literatures,[2] but only one total synthesis of **1** and **2** has been reported to date.[3] Recently we developed an efficient methodology for the construction of polypropionate segment.[4] As an extension of the study, synthesis of **1** was examined.



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

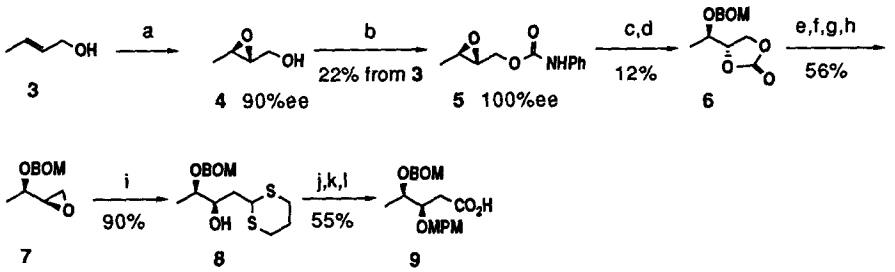


Scheme 1

Our synthetic strategy is based on the retrosynthetic analysis shown in **Scheme 1**. Dissociation of two ester linkage in **1** gives fragments **A** and **B**. Further division of fragment **A** gives three fragments **C**, **D**, and **E**, in which **C** and **E** are considered to be combined with **D** by nucleophilic opening of two different epoxides in **D**. The terminal epoxide in **D** is masked as a protected diol until an appropriate stage. It seems to be possible to synthesize fragments **B**, **C**, and **E** by using titanium-mediated asymmetric epoxidation[5] (hereafter referred to as A.E.) as a key step and to introduce the stereochemistry of fragment **D** by [2,3] Wittig rearrangement we reported.[4d] In this and following communications, we describe preparations of optically active fragments and synthesis of **1**, respectively.

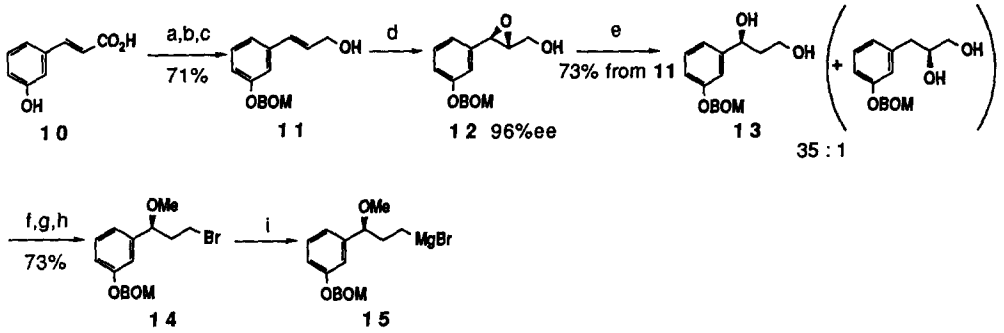
Synthesis of fragment **B** started with crotyl alcohol (**3**) as shown in **Scheme 2**. A.E. of **3** gave epoxy alcohol **4**[6] of 90% ee. Treatment of **4** with phenyl isocyanate gave carbamate **5**, which was recrystallized to

optical purity. Acid treatment of **5** followed by hydroxy protection gave carbonate **6**, which was further converted into epoxide **7** by the sequence: i) alcoholysis of carbonate, ii) protection of the resulting primary hydroxy group as a pivalate, iii) mesylation of secondary hydroxy group, iv) reductive removal of pivaloyl group, and v) epoxide formation. One carbon elongation to **8** was achieved by the treatment of **7** with 2-lithio-1,3-dithiane. Transformation of **8** into the desired carboxylic acid **9** corresponding to fragment **B** was achieved in three steps: i) protection of hydroxy group as a MPM ether,[7] ii) hydrolysis of dithioacetal, and iii) oxidation of the resulting aldehyde.



a) $Ti(O^iPr)_4$, (-)-DET, TBHP, MS 4Å; b) phenyl isocyanate, Et_3N then recrystallization from AcOEt; c) $HClO_4$; d) BOMCl, EtN^iPr_2; e) K_2CO_3, MeOH; f) $(CH_3)_3CCOCl$, Et_3N then MsCl; g) DIBAL; h) ^tBuOK; i) 2-lithio-1,3-dithiane; j) MPMCl, NaH; k) MeI, $CaCO_3$; l) $NaClO_2$, 2-methyl-2-butene

Scheme 2



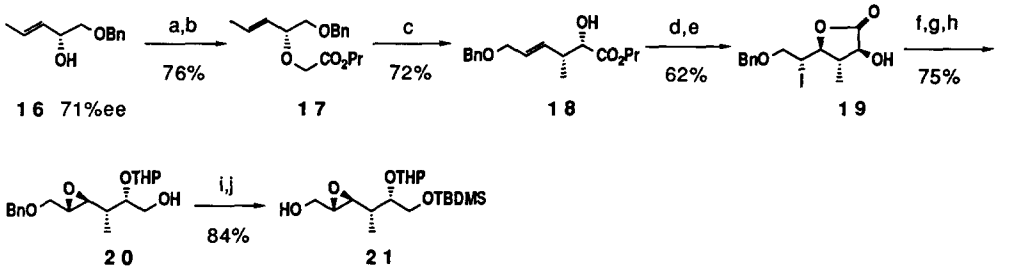
a) EtOH, H_2SO_4; b) BOMCl, EtN^iPr_2; c) DIBAL; d) $Ti(O^iPr)_4$, (-)-DIPT, TBHP, MS 4Å; e) Red-al; f) TsCl, Et_3N; g) MeI, NaH; h) NaBr; i) Mg

Scheme 3

For fragment **C**, *m*-hydroxycinnamic acid (**10**) was employed as a starting material (**Scheme 3**). Conversion of **10** to allylic alcohol **11** was carried out in a conventional manner. A.E. of **11** gave epoxy alcohol **12** with high enantioselectivity (96% ee). Red-al reduction[8] of **12** proceeded with high regioselectivity (1,3- : 1,2-diol = 35 : 1) to give diol **13**.[9] Conversion of **13** to **14** was achieved by the sequence: i) tosylation of primary hydroxy group, ii) methylation of secondary hydroxy group, and iii) replacement of the tosylate with bromide. Treatment of **14** with magnesium gave **15** to be used for the coupling with fragment **D**.

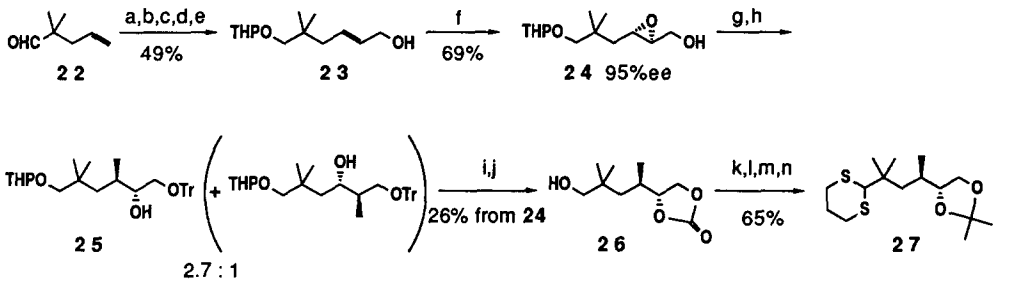
Synthesis of fragment **D** started with (2*R*,3*E*)-1-benzyloxy-3-buten-2-ol (**16**) of 71% ee,[10] which was obtained by kinetic resolution of *dl*-**16**[4c] (**Scheme 4**). Compound **16** was converted into ester **17** according to

the reported procedure.[11] Titanium-mediated [2,3] Wittig rearrangement of **17** afforded ω-benzyloxylated hydroxy ester **18** with quantitative chirality transfer together with high *syn* selectivity.[12] After alkaline hydrolysis, **18** was subjected to iodolactonization.[13] Lactone **19** was converted into hydroxy epoxide **20** in three steps; i) protection of hydroxy group as a THP ether,[14] ii) methanolysis of lactone along with epoxide formation, and iii) LAH reduction of the resulting methyl ester. Hydroxy protection as a TBDMS ether followed by hydrogenolysis afforded epoxy alcohol **21** which was a synthetic equivalent of fragment **D**.



a) $BrCH_2CO_2H$, NaH; b) ^iPrI, Na_2CO_3; c) LDA then Cp_2TiCl_2; d) KOH, MeOH-H_2O; e) I_2; f) DHP, PPTS; g) K_2CO_3, MeOH; h) LAH; i) TBDMSCl, Et_3N, DMAP; j) H_2, Pd/C

Scheme 4



a) $NaBH_4$; b) DHP, PPTS; c) OsO_4, $NaIO_4$; d) $(EtO)_2P(O)CH_2CO_2Et$, NaH; e) DIBAL; f) $Ti(O^iPr)_4$, (+)-DET, TBHP, MS 4Å; g) TrCl, Et_3N, DMAP; h) MeMgBr, CuI; i) CSA, MeOH; j) $COIm_2$ then chromatographic separation; k) Swern oxdn.; l) 1,3-propanedithiol, $BF_3{\cdot}OEt_2$; m) K_2CO_3, MeOH; n) 2,2-dimethoxypropane, PPTS

Scheme 5

Fragment **E** was derived from easily available olefin **22**.[15] As shown in **Scheme 5**, **22** was first converted into allylic alcohol **23** by the sequence: i) reduction of aldehyde, ii) protection of the resulting hydroxy group as a THP ether,[14] iii) oxidative cleavage of olefin, iv) two carbon elongation by Wittig-Honer olefination,[16] and v) DIBAL reduction. A.E. of **23** gave epoxide **24** of 95% ee. After hydroxy protection as a trityl ether, **24** was exposed to methylmagnesium bromide in the presence of CuI giving a mixture of **25** and its regioisomer in a ratio of 2.7 : 1.[9,17] After acid hydrolysis, compound **25** and its regioisomer were treated with carbonyldiimidazole and the resulted regioisomeric carbonates were separated by column chromatography (SiO_2) to give **26**. Dithioacetal **27** to be used as fragment **E**, was elaborated from **26** in four steps; i) Swern oxidation,

ii) dithioacetalization of the resulting aldehyde, iii) alcoholysis of carbonate, and iv) protection of the resulting diol as an acetonide.

With fragments **B**, **C**, **D**, and **E** in hand, the stage was set for the construction of **1**, which will be described in the following communication.

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9) The isomers ratio was determined by ^{1}H NMR (400MHz, $CDCl_3$) analysis after the acetylation of hydroxy group.

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