Pergamon

Tetrahedron Letters 40 (1999) 1911–1914

TETRAHEDRON LETTERS

Partial Synthesis of Ciguatoxin (5*R*)-ABC Segment

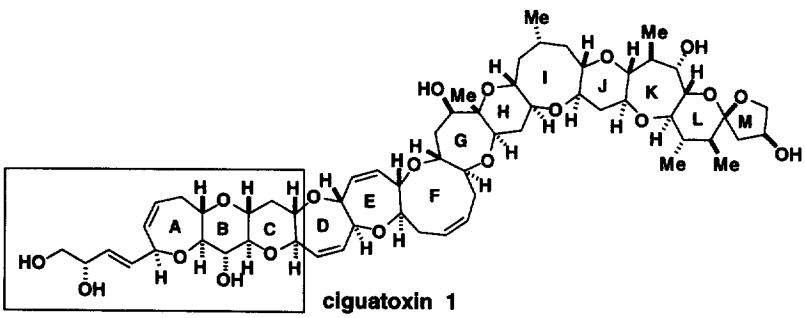
Rungnapha Saeeng and Minoru Isobe*

Laboratory of Organic Chemistry, School of Bioagricultural Sciences, Nagoya University
Chikusa, Nagoya 464-8601, Japan
* isobem@agr.nagoya-u.ac.jp

Received 7 December 1998; revised 24 December 1998; accepted 25 December 1998

Abstract : An ABC segment of ciguatoxin has been synthesized in a correct enantiomeric form from a D-glucose derivative based on the route for the opposite enantiomer by switching enantiomerism of a pseudosymmetric intermediate. This route, however, has been improved in several steps and ended up with a vinylthioether group for future extension toward the D ring of ciguatoxin molecule.
© 1999 Elsevier Science Ltd. All rights reserved.
Key words -:- ciguatoxin, acetylene biscobalthexacarbonyl complex

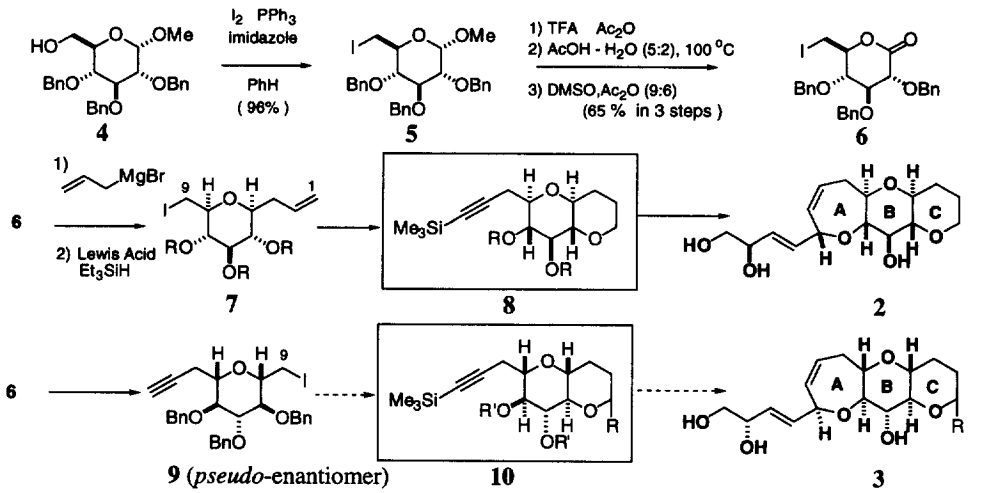
Ciguatoxin **1**, a polyether compound found in various sea food as a principal toxin causing ciguatera poisoning, is known to be originally produced by *Gambierdiscus toxicus*.[1] It is available in small quantities from nature, and thus only little has been studied from a chemical and bioorganic point of views about **1**. We became interested in the synthesis of **1** as one of the most challenging targets as well as the source compound collecting biological information. During the earlier course of our synthetic studies directed toward ciguatoxin, we have already established a series of methodologies; (i) C-glycosidation of an alkynyl group onto di- or tetrahydropyranyl ring of sugars at the C-1 position exclusively in *alpha* orientation,[2] (ii) epimerization of this alkynyl group into the *beta* orientation via biscobalthexacarbonyl complex,[3] (iii) re-cyclization of the dihydropyranyl ring to medium-sized ether ring with high stereoselectivity.[4] These reactions include cationic intermediates that are stabilized either by σ–π conjugation with silicon atom or by Nicholas effect[5] with the acetylene biscobalthexacarbonyl complex.[6] We reported a synthesis of (-)-ABC segments, namely (*2R,5S*)-ABC segment of **1** and (*2S,5S*)-diastereomer in the opposite enantiomeric form,[7] because we had started synthetic studies before its absolute configuration has been established.[8] This synthesis, however, was designed so that one can synthesize the other enantiomer, (+)-ABC segment by switching the *pseudoenantiomerism*, that is described in this paper with further improvements.



ciguatoxin 1

0040-4039/99/$ - see front matter © 1999 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(99)00041-6

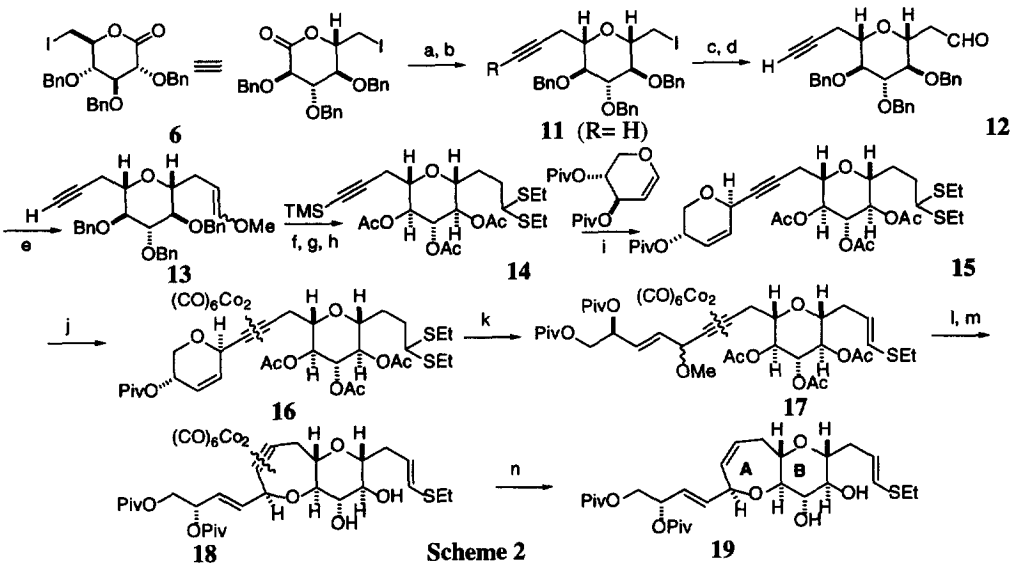
Yasumoto *et al.* reported that the absolute configuration of ciguatoxin is (*2S,5R*)-configuration as shown in **1**.[8] In **Scheme 1** key steps summarize the synthesis of ambient enantiomers by comparing our own previous opposite (*2R,5S*)-enantiomer, that has partly been improved. Namely, the methyl-α-D-2,3,4-tri-*O*-benzylglucoside **4** was converted into the iodolactone **6**, further three-carbon elongation and subsequent reduction at the C-1 position gave the C-allylated intermediate **7** for the synthesis of the opposite enantiomer **2**, (*2R,5S*)-ABC segment via silylacetylene **8**. On the other hand, one can turn over the intermediate **7** to provide a *pseudo*-enantiomer related to **9**, which one can synthesize from **6**. In addition to a direct introduction of an acetylenic group to **9**, a substituent R on the C-ring of **10** might be useful for further elongation toward the D-ring of **1** in later steps. Thus, we designed the synthesis of (*2S,5R*)-ABC segment **3** equivalents, **19** and **22** in **Scheme 2** and **3**.[9]



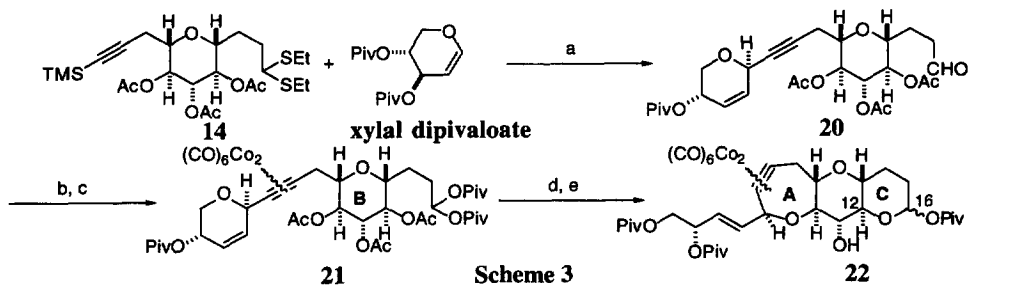
Scheme 1

A direct introduction of the acetylenic group was examined with the iodolactone **6** as a precursor for the *pseudo*-enantiomer series, and propargyl anion was employed as a better candidate for **9**. Addition of propargylmagnesium bromide[10] to the lactone **6** at -78 °C in diethyl ether was followed by stirring for 1.5 hr at this temperature, and the obtained product was successively dissolved in CH_3CN and reduced with Et_3SiH and $BF_3{\bullet}OEt_2$ at -78 °C to yield the acetylene **11** (R= H, in 60 % in 2 steps: mp. 93 °C: NMR, H-9 δ 2.05 ppm *t*, *J*= 3.0 Hz; C-9 δ 71.3, C-8 δ 87.2 ppm and no allenic signal around δ 210 ppm).[11,12] In this case, the iodide moiety survived at such a low temperature with propargylmagnesium anions, but the propargyllithium reagent afforded an elimination product.[13] Addition of the silylated propargylmagnesium bromide was not employed to avoid the potential formation of allene corresponding to this propargylic anion. For example, excess Grignard reagent (4.5 equiv) provided the magnesium acetylide of **11** (R = MgBr) without complication to give exclusively **11**. As a synthetic intermediate for (*5R*)-ABC segment as well as for the total synthesis toward **1**, we have to provide some functional groups on a C-ring precursor for future elongation toward the D-ring. We have decided to elongate a two-carbon unit along this line. So the iodide **11** was once displaced by cyanide and a nitrile product (mp. 102 °C) was then treated with DIBAL-H to convert into the corresponding aldehyde **12** (mp. 106 °C in 90 % overall yield in 2 steps). Wittig reaction of this aldehyde **12** gave the vinyl ether **13** as a

mixture of *E/Z* olefins (in a ratio of 1.6:1, J = 13.5 Hz and 7.0 Hz, respectively). Debenzylation of this mixture under Fuji's protocol[14] effected the vinyl ether moiety as well to provide a polar triol-thioacetal derivative, which was isolated after acetylation and silylation in the form of **14** (mp. 87 °C). C-Glycosidation of this silylacetylene **14** with D-xylal yielded the 1,4-*anti* product[15] **15** (m/z 642, M^+; $[\alpha]_D^{26}$ +62.8 (c 0.47, $CHCl_3$)) in 40 % yield, and the acetylene moiety was converted to its corresponding biscobalthexacarbonyl complex **16** (m/z 927, M+1$^+$; NMR H-5 δ 5.34, dd, J = 4.0, 2.0 Hz: $[\alpha]_D^{27}$ -104 (c 0.05, $CHCl_3$)) in 97 % yield.



Reagents and conditions. a) $HC{\equiv}CCH_2MgBr$ (4.5 equiv.) in ether at -78 °C. b) $BF_3{\bullet}OEt_2$, Et_3SiH, MeCN (60 % in 2 steps). c) NaCN in DMSO. d) DIBALH, CH_2Cl_2 (90 % in 2 steps). e) $[Ph_3PCH_2OMe]^+Cl^-$, *t*-BuLi (68 %). f) $BF_3{\bullet}OEt_2$, EtSH, CH_2Cl_2. g) EtMgBr, TMSCl. h) Ac_2O, Py, CH_2Cl_2 (57 % in 3 steps). i) $SnCl_4$, CH_2Cl_2(40 %). j) $Co_2(CO)_8$ (97 %). k) Piv_2O, TfOH in CH_2Cl_2 then MeOH (73 %). l) K_2CO_3, MeOH (98 %). m) TfOH, MS-4A°, (41 %, 70 % yield based on recovered **17**). n) *n*-Bu_3SnH, benzene, 60 °C (63 %).



Reagents and conditions. a) $SnCl_4$ in CH_2Cl_2 at -20 °C, 2 hr (96 %). b) $Co_2(CO)_8$ (97 %). c) Piv_2O, TfOH in CH_2Cl_2 then MeOH (48 %). d) K_2CO_3, MeOH (50 %). e) $BF_3{\bullet}OEt_2$, EtSH, CH_2Cl_2 (10 %).

Opening of the dihydropyran ring of **16** was facilitated by pivalic anhydride in the presence of trifluoromethane sulfonic acid in dichloromethane and the product was isolated after quenching the cation intermediate with methanol to give a mixture of diastereomers **17**. The acetate was hydrolyzed with potassium carbonate to the corresponding tri-ol, that was treated with trifluoromethane sulfonic acid in the presence of molecular sieves to

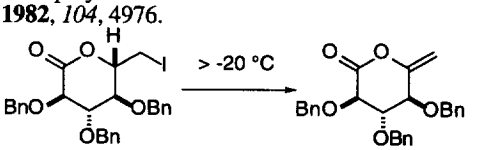
provide the 7 membered ether **18** (m/z 826, M+1; NMR H-5, δ 5.04 d, *J*= 4.7 Hz: $[\alpha]_D^{27}$ +111 (c 0.04, $CHCl_3$)). The oxepene A ring was synthesized by decomplexation by heating **18** with tributyltin hydride in benzene at 60 °C for 2 hr to isolate the product **19** ($[\alpha]_D^{26}$ +57.5 (c 0.05, MeOH))showing supporting data.[16]

In **Scheme 3** an alternative route to ABC segment is shown by starting from the same C-glycosidation of **14** with xylal for 2 hr (*longer* period of time than the case of **15**), while the dithioacetal underwent hydrolysis to give the corresponding aldehyde **20** (δ 9.78 ppm *s*). In this series, the same cobalt-assisted cation cyclization of **21** turned out to be lower yield (10 %) to provide **22** (H16 δ 4.8 ppm showed NOE with H12).

The synthesis of the correct enantiomer of ciguatoxin (*5R)*-ABC segment has now been achieved based on the enantiomeric switching method starting from a D-glucose derivative. Further studies toward the total synthesis of **1** are now in progress.

Acknowledgment This research was financially supported by a Grant-In-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture and by JSPS-RFTF. R. S. is grateful to Monbusho Scholarship during her graduate studies for PhD. Special thanks are due to Drs. S. Hosokawa and B. Kirschbaum for advice and to Mr. K. Koga and Mr. S. Kitamura of this school for analytical instrumentation.

References and Notes

1 a) Murata, M.; Legrand, A. M.; Ishibashi, Y.; Fukui, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1990**, *112*, 4380-4386.
2 a) Ichikawa, Y.; Isobe, M.; Konobe, M.; Goto, T. *Carbohydrate Research*, **1987**, *171*, 193-199. b) Tsukiyama, T.; Isobe, M. *Tetrahedron Lett.*, **1992**, *33 (#51)*, 7911-7914.
3 a) Tanaka, S.; Tsukiyama, T.; Isobe, M. *Tetrahedron Lett.* **1993**, *34*, 5757-5760. b) Tanaka, S. Isobe, M. *Tetrahedron* **1994**, *50*, 5633-5644. c) Tanaka, S.; Isobe, M. *Tetrahedron Lett.* **1994**, *35*, 7801-7804. d) Tanaka, S.; Tatsuta, T.; Yamashita, O.; Isobe, M. *Tetrahedron* **1994**, *50*, 12883-12894.
4 a) Isobe, M.; Yenjai, C.; Tanaka, S. *Synlett* **1994**, 916-918. b) Yenjai, C.; Isobe M. *Tetrahedron*, **1998**, *54*, 2509-2520.
5 a) Nicholas, K. M.; Pettit, R. *Tetrahedron Lett.* **1971**, 3475-3478. b) Seyferth, D.; Nestle, M. O.; Wehman, A. T. *J. Am. Chem. Soc.* **1975**, *97*, 7417-7426. c) Nicholas, K. M. *Acc. Chem. Res.* **1987**, *20*, 207-214, and references cited therein. d) Muehldorf, A. V.; Guzman-Perez, A.; Kluge, A. F.; *Tetrahedron Lett.* **1994**, *35*, 8755-8758.
6 Isobe, M.; Nishizawa, R.; Hosokawa, S.; Nishikawa, T. *J. Chem. Soc., Chem. Comm. in press.*
7 a) Hosokawa, S.; Isobe, M. *Synlett*, **1995**, *(#11)*, 1179-1180. b) Hosokawa, S.; Isobe M. *Synlett*, **1996**, *(#4)* 351-352. c) Isobe, M.; Hosokawa, S.; Kira, K. *Chem. Lett.*, **1996**, 473-474.
8 a) Satake, M. Morohashi, A.; Oguri, H.; Oishi, T.; Hirama, M.; Harada, N.; Yasumoto, T. *J. Am. Chem. Soc.*, **1997**, *119*, 11325-11326. b) Oguri, H.; Hishayama, S.; Sato. O.; Oishi, T.; Hirama, M.; Murata, M.; Yasumoto, T.; Harada, N. *Tetrahedron*, **1997**, *53*, 3057-3072.
9 Syntheses of the AB(C) segments have been reported in ref. # *7a, 7b, 7c, 8b* and Oka, T.; Fujiwara, K.; Murai, A. *Tetrahedron*, **1998**, *54*, 21-44.
10 Suzuki, M.; Morita, Y.; Noyori, R. *J. Org. Chem.*, **1990**, *55*, 441-449.
11 The debenzylation condition (BF_3•OEt_2, EtSH) affected a silylacetylene derivative corresponding to **13** (provided from **11** R= $SiMe_3$), and thus **11** (R = H) was employed.
12 Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976.
13 In this case, an alternative nucleophile [Me_3Si-C≡CCH_2Li generated from Me_3Si-C≡CMe and *n*-BuLi] did not add to this lactone at -78 °C. At a higher temperature (-20 °C) an elimination took place, instead, to give the vinyllactone as follows.


14 (a) Fuji, K.; Ichikawa, K.; Node, M.; Fujita, E. *J. Org. Chem.* **1979**, *44*, 1661. (b) Daly, S. M.; Armstrong, R. W. *Tetrahedron Lett.* **1989**, *30*, 5713.
15 Hosokawa, S.; Kirschbaum, B.; Isobe, M. *Tetrahedron Lett.*, **1998**, *39*, 1917-1920.
16 Compound **19**: ^{1}H-NMR (400 MHz, $CDCl_3$), δ 1.29 (3H, *t*, *J* = 7.5 Hz -SCH_2CH_3), 2.68 (2H, *q*, *J* = 7.5 Hz -SCH_2CH_3), 3.27 (1H, *ddd*, *J* = 9.0, 8.5, 4.5 H_9), 3.28 (1H, *t*, *J* = 9.0 Hz H_{10}), 3.49 (1H, *t*, *J* = 9.0 Hz H_{12}), 3.56 (1H, *t*, *J* = 9.0 Hz H_{11}), 4.09 (1H, *ddd*, *J* = 12, 6.5 4 Hz H_{1a}), 4.25 (1H, *dd*, *J* = 12, 4 Hz H_{1b}), 4.51 (1H, *m*, *H-5*), 5.85 (1H, *ddt*, *J* = 15.5, 5.5, 1 Hz H_4), 6.04 (1H, *d*, *J* = 9.5 Hz H_{16}).