

## Asymmetric Synthesis of the A-ring Part of Ciguatoxin by the Strategy Based on Diastereoselective Hydroboration and Ring Closing Metathesis

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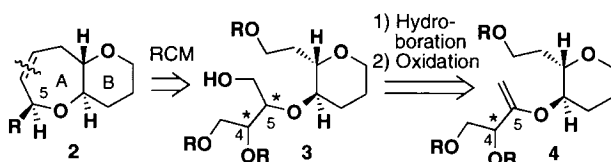
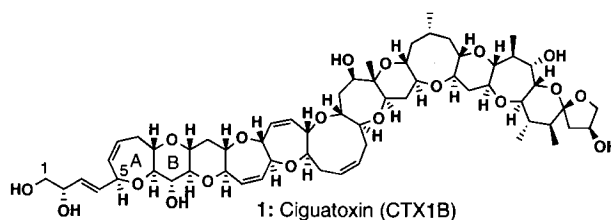
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Asymmetric synthesis of the A-ring part of a marine toxin ciguatoxin (CTX1B) was achieved by the strategy based on ring closing metathesis (RCM), where introduction of the C5 asymmetric center was performed by diastereocontrolled hydroboration of a vinyl ether moiety.

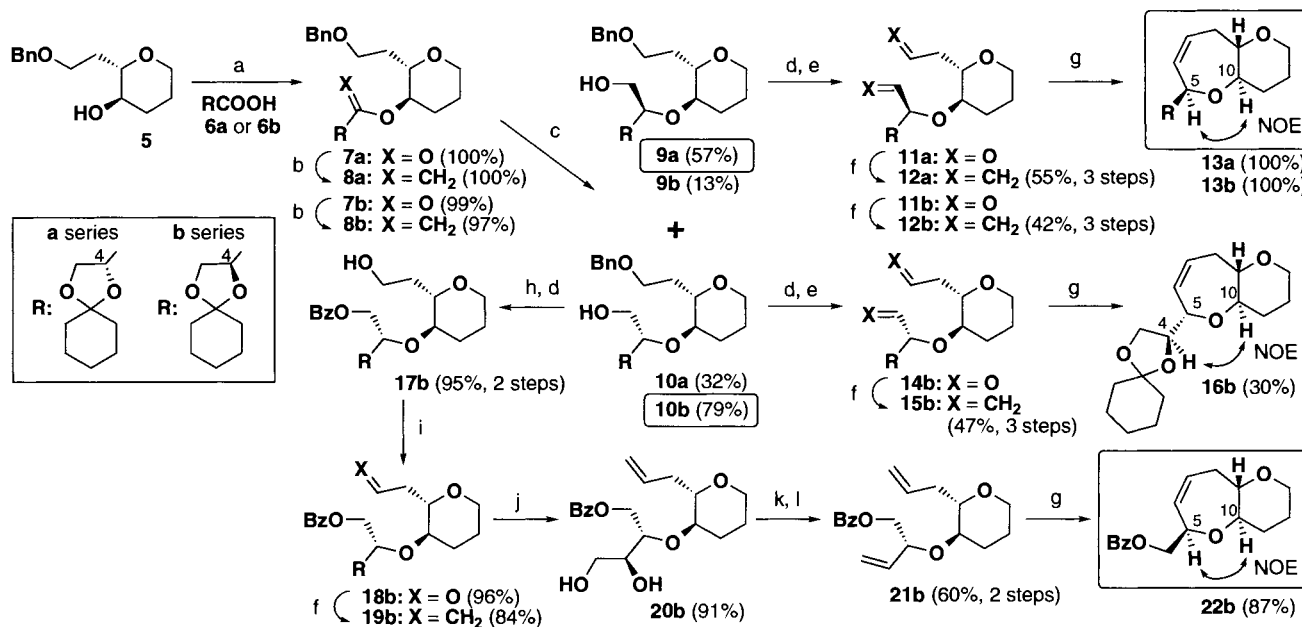
Ciguatoxin (CTX1B) **1**, which is one of the causative toxins of food poisoning, ciguatera, attracts much attention of synthetic chemists in its complex structure and strong bioactivity.<sup>1-5</sup> As a part of our synthetic study on **1**,<sup>2</sup> we have studied asymmetric synthesis of the A-ring part of **1**.<sup>3,4</sup> based on ring closing metathesis (RCM).<sup>6</sup> During our study, Hirama group has reported the synthesis of the same part by C5<sup>7</sup>-stereoselective RCM.<sup>5</sup> We describe here an alternative approach to the stereocontrol at C5 in the synthesis of the A-ring part of **1**.

Our synthetic plan is outlined in Scheme 1, where simple model compound **2** was the target. In this plan, the stereocontrol at C5 is required at the stage before RCM. Consequently, we intended to synthesize the precursor **3** stereoselectively by hydroboration of vinyl ether **4** having an asymmetric center at C4<sup>7</sup> as a chiral auxiliary according to McGarvey's method.<sup>8</sup>



Scheme 1.

First, vinyl ether **8a** was prepared by esterification of chiral oxane **5**<sup>9</sup> with carboxylic acid **6a** derived from D-mannitol<sup>10</sup> followed by olefination of the resultant ester **7a** with Tebbe reagent<sup>11</sup> (Scheme 2). Hydroboration of **8a** with  $\text{BH}_3 \cdot \text{THF}$  followed by oxidation gave ethers **9a** and **10a** in 57% and 32% yields, respectively.<sup>12</sup> The major product **9a** was converted to



**Scheme 2.** Reagents and Conditions: a) **6** (1.2-1.3 eq), DCC (2.0 eq), DMAP (0.5 eq),  $\text{CH}_2\text{Cl}_2$ , 22-24 °C, 0.5-2 h; b)  $\text{Cp}_2\text{TiCl}_2$  (1.5 eq),  $\text{AlMe}_3$  (3 eq), toluene, 23 °C, 3 d, then **7**, THF-toluene (1:6-9), 0  $\rightarrow$  23 °C, 20-30 min; c) [reaction of **8a**]:  $\text{BH}_3 \cdot \text{THF}$  (3.0 eq), THF, -30 °C, 14 h, then 5M NaOH (9.0 eq), 30%  $\text{H}_2\text{O}_2$  (9.0 eq), 0  $\rightarrow$  25 °C, 11 h; [reaction of **8b**]:  $\text{BH}_3 \cdot \text{THF}$  (1.5 eq), THF, 0 °C, 40 min, then 5M NaOH (4.5 eq), 30%  $\text{H}_2\text{O}_2$  (4.5 eq), 0  $\rightarrow$  22 °C, 13 h; d)  $\text{H}_2$ , Pd/C, EtOH or MeOH, 22-25 °C, 4-19 h; e) Dess-Martin periodinane (5.1-5.5 eq),  $\text{CH}_2\text{Cl}_2$ , 22-24 °C, 1.5-3 h; f)  $\text{Ph}_3\text{P}=\text{CH}_2$  (2.5-6.2 eq), THF, -78  $\rightarrow$  0 °C, 0.7-13 h; g)  $(\text{C}_3\text{P})_2\text{Cl}_2\text{Ru}=\text{CHPh}$  (0.3-0.9 eq),  $\text{CH}_2\text{Cl}_2$ , reflux, 1-6 h; h)  $\text{BzCl}$  (5.0 eq), DMAP (0.5 eq), pyridine, 25 °C, 3.5 h; i)  $(\text{COCl})_2$  (4.5 eq), DMSO (7.2 eq),  $\text{CH}_2\text{Cl}_2$ , -78 °C, 25 min, then  $\text{Et}_3\text{N}$  (15 eq), -78  $\rightarrow$  0 °C, 30 min; j) 3M HCl-THF (1:1), 27 °C, 30 h; k)  $\text{PPh}_3$  (8 eq),  $\text{I}_2$  (6.1 eq), imidazole (8.1 eq), toluene, 26 °C, 19 h, then reflux, 20.5 h; l) Zn (25 eq), EtOH-aq.  $\text{NH}_4\text{Cl}$  (5:1), 26 °C, 6 h.

the bicyclic compound **13a**, corresponding to the AB-ring fragment of **1**, through a 4-step sequence [(i) debenzoylation, (ii) Dess-Martin oxidation,<sup>13</sup> (iii) Wittig reaction, and (iv) RCM with Grubbs' catalyst]<sup>6</sup> in a 55% total yield. Observation of NOE (H5/H10) confirmed the desired stereochemistry at C5, which agreed with McGarvey's selectivity.<sup>8</sup>

Next, we examined C4-epimeric **8b**, which was synthesized from **6b** originated from L- $\gamma$ -gulonolactone<sup>10</sup> in the similar manner to **8a**. When **8b** was subjected to hydroboration with BH<sub>3</sub>·THF followed by oxidation, **9b** and **10b** were produced in 13% and 79% yields, respectively.<sup>12</sup> These **9b** and **10b** were converted to bicyclic ethers **13b** and **16b**, respectively, according to the above method. Existence of NOE (H5/H10) in **13b** and NOE (H4/H10) in **16b** verified their stereochemistry. After all, **8b** displayed the improved McGarvey's stereoselectivity,<sup>8</sup> though the major product **10b** was not available directly in its stereochemistry at C5 for the above 4-step route to the AB-ring fragment of **1**.

Then, an alternative route for the A-ring construction starting from **10b** was investigated. Protection of **10b** with BzCl followed by debenzoylation gave alcohol **17b** (95%), which was converted to **19b** through an oxidation-Wittig reaction process (81%, 2 steps). After removal of cyclohexylidene acetal (91%), diol **20b** was converted to diene **21b** (60%) by iodination and elimination.<sup>14</sup> Final RCM step proceeded smoothly to produce bicyclic **22b** (87%), whose stereochemistry was confirmed by NOE (H5/H10).

Thus, asymmetric synthesis of the A-ring part of **1** was achieved by two complementary routes based on RCM as well as diastereocontrolled hydroboration.

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#### References and Notes

- For reviews on ciguatoxins and related compounds, see: a) T. Yasumoto and M. Murata, *Chem. Rev.*, **93**, 1897 (1993). b) P. J. Scheuer, *Tetrahedron*, **50**, 3 (1994). For absolute configuration of **1**, see: c) M. Satake, A. Morohashi, H. Oguri, T. Oishi, M. Hiramata, N. Harada, and T. Yasumoto, *J. Am. Chem. Soc.*, **119**, 11325 (1997).
- For our synthetic studies on **1**, see: a) T. Oka and A. Murai, *Chem. Lett.*, **1994**, 1611. b) T. Oka, K. Fujiwara, and A. Murai, *Tetrahedron*, **52**, 12091 (1996). c) H. Atsuta, K. Fujiwara, and A. Murai, *Synlett*, **1997**, 307. d) T. Oka, K. Fujiwara, and A. Murai, *Tetrahedron Lett.*, **38**, 8053 (1997). e) T. Oka and A. Murai, *Tetrahedron*, **54**, 1 (1998). f) T. Oka, K. Fujiwara, and A. Murai, *Tetrahedron*, **54**, 21 (1998).
- For the syntheses of the A-ring part of **1**, see: a) T. Suzuki, O. Sato, M. Hiramata, Y. Yamamoto, M. Murata, T. Yasumoto, and N. Harada, *Tetrahedron Lett.*, **32**, 4505 (1991). b) O. Sato and M. Hiramata, *Synlett*, **1992**, 705. c) S. Hosokawa and M. Isobe, *Synlett*, **1995**, 1179. d) H. Oguri, S. Hishiyama, T. Oishi, and M. Hiramata, *Synlett*, **1995**, 1252. e) S. Hosokawa and M. Isobe, *Synlett*, **1996**, 351. f) H. Oguri, S. Hishiyama, O. Sato, T. Oishi, M. Hiramata, M. Murata, T. Yasumoto, and N. Harada, *Tetrahedron*, **53**, 3057 (1997). g) M. Isobe, R. Nishizawa, S. Hosokawa, and T. Nisikawa, *Chem. Commun.*, **1998**, 2665. h) S. Hosokawa and M. Isobe, *J. Org. Chem.*, **64**, 37 (1999). i) K. Maeda, T. Oishi, H. Oguri, and M. Hiramata, *Chem. Commun.*, **1999**, 1063. j) H. Oguri, S.-i. Tanaka, S. Hishiyama, T. Oishi, M. Hiramata, T. Tsumuraya, Y. Tomioka, and M. Mizugaki, *Synthesis*, **1999**, 1431. k) R. Saeng and M. Isobe, *Tetrahedron Lett.*, **40**, 1911 (1999). See also Ref. 2d, 2f, and 5.
- For other synthetic studies on **1**, see: a) E. Alvarez, M. T. Díaz, R. Pérez, and J. D. Martín, *Tetrahedron Lett.*, **32**, 2241 (1991). b) J. L. Ravelo, A. Regueiro, and J. D. Martín, *Tetrahedron Lett.*, **33**, 3389 (1992). c) M. Sasaki, A. Hasegawa, and K. Tachibana, *Tetrahedron Lett.*, **34**, 8489 (1993). d) M. Sasaki, M. Inoue, and K. Tachibana, *J. Org. Chem.*, **59**, 715 (1994). e) E. Alvarez, M. T. Díaz, R. Pérez, J. L. Ravelo, A. Regueiro, J. A. Vera, D. Zurita, and J. D. Martín, *J. Org. Chem.*, **59**, 2848 (1994). f) T. Oishi, M. Shoji, K. Maeda, N. Kumahara, and M. Hiramata, *Synlett*, **1996**, 1165. g) T. Oishi, M. Shoji, N. Kumahara, and M. Hiramata, *Chem. Lett.*, **1997**, 845. h) T. Oishi, K. Maeda, and M. Hiramata, *Chem. Commun.*, **1997**, 1289. i) M. Inoue, M. Sasaki, and K. Tachibana, *Tetrahedron Lett.*, **38**, 1611 (1997). j) E.-i. Ami, H. Kishimoto, H. Ohru, and H. Meguro, *Biosci. Biotech. Biochem.*, **61**, 2019 (1997). k) M. Satake, A. Morohashi, H. Oguri, T. Oishi, M. Hiramata, N. Harada, and T. Yasumoto, *J. Am. Chem. Soc.*, **119**, 11325 (1997). l) M. Inoue, M. Sasaki, and K. Tachibana, *Angew. Chem., Int. Ed. Engl.*, **37**, 965 (1998). m) M. Sasaki, T. Noguchi, and K. Tachibana, *Tetrahedron Lett.*, **40**, 1337 (1999). n) T. Oishi, M. Maruyama, M. Shoji, K. Maeda, N. Kumahara, S.-i. Tanaka, and M. Hiramata, *Tetrahedron*, **55**, 7471 (1999). o) M. Sasaki, M. Inoue, K. Takamatsu, and K. Tachibana, *J. Org. Chem.*, **64**, 9399 (1999). p) M. Inoue, M. Sasaki, and K. Tachibana, *J. Org. Chem.*, **64**, 9416 (1999). q) M. Inoue, M. Sasaki, and K. Tachibana, *Tetrahedron*, **55**, 10949 (1999). r) T.-Z. Liu and M. Isobe, *Synlett*, **2000**, 266. s) M. Sasaki, K. Noguchi, H. Fuwa, and K. Tachibana, *Tetrahedron Lett.*, **41**, 1425 (2000).
- a) H. Oguri, S. Sasaki, T. Oishi, and M. Hiramata, *Tetrahedron Lett.*, **40**, 5405 (1999). b) H. Oguri, S. Tanaka, T. Oishi, and M. Hiramata, *Tetrahedron Lett.*, **41**, 975 (2000).
- For reviews on ring-closing metathesis, see: a) R. H. Grubbs and S. Chang, *Tetrahedron*, **54**, 4413 (1998). b) M. Schuster and S. Blechert, *Angew. Chem., Int. Ed. Engl.*, **36**, 2036 (1997). c) R. H. Grubbs, S. J. Miller, and G. C. Fu, *Acc. Chem. Res.*, **28**, 446 (1995). For recent applications to 7-membered cyclic ethers, see: d) W. J. Zuercher, M. Hashimoto, and R. H. Grubbs, *J. Am. Chem. Soc.*, **118**, 6634 (1996). e) J. S. Clark and J. G. Kettle, *Tetrahedron Lett.*, **38**, 123 (1997). f) R. J. Linderman, J. Siedlecki, S. A. O'Neill, and H. Sun, *J. Am. Chem. Soc.*, **119**, 6919 (1997). g) M. Delgado and J. D. Martín, *Tetrahedron Lett.*, **38**, 6299 (1997). h) M. T. Crimmins and A. L. Choy, *J. Org. Chem.*, **62**, 7548 (1997). i) F. P. J. T. Rutjes, T. M. Kooistra, H. Hiemstra, and H. E. Schoemaker, *Synlett*, **1998**, 192. j) M. Stefinovic and V. Snieckus, *J. Org. Chem.*, **63**, 2808 (1998). k) H. Ovaa, M. A. Leeuwenburgh, H. S. Overkleeft, G. A. Van der Marel, and J. H. Van Boom, *Tetrahedron Lett.*, **39**, 3025 (1998). l) T. Oishi, Y. Nagumo, and M. Hiramata, *Synlett*, **1997**, 980. m) T. Oishi, Y. Nagumo, and M. Hiramata, *Chem. Commun.*, **1998**, 1041. n) L. Eriksson, S. Guy, P. Perlmutter, and R. Lewis, *J. Org. Chem.*, **64**, 8396 (1999). o) M. A. Leeuwenburgh, C. Kulker, H. S. Overkleeft, G. A. Van der Marel, and J. H. Van Boom, *Synlett*, **1999**, 1945.
- Position numberings in this letter are according to those of CTX1B.
- a) G. J. McGarvey and J. S. Bajwa, *Tetrahedron Lett.*, **26**, 6297 (1985). See also: b) W. C. Still and J. C. Barrish, *J. Am. Chem. Soc.*, **105**, 2487 (1983). c) M. M. Midland and Y. C. Kwon, *J. Am. Chem. Soc.*, **105**, 3725 (1983). d) K. N. Houk, N. G. Rondan, Y.-D. Wu, J. T. Mets, and M. N. Paddon-Row, *Tetrahedron*, **40**, 2257 (1984).
- Oxane **5** was prepared through a 6-step process [MOMCl, *i*-Pr<sub>3</sub>NEt; OsO<sub>4</sub>, NMO; NaIO<sub>4</sub>; NaBH<sub>4</sub>; BnBr, *t*-BuOK, TBAI; 6M HCl-THF (1:1); 83% total yield] from (2*S*, 3*R*)-2-(2-propenyl)-3-hydroxyoxane (98% ee) which was synthesized according to the following paper: K. Fujiwara, K. Saka, D. Takaoka, and A. Murai, *Synlett*, **1999**, 1037.
- Carboxylic acids **6a** and **6b** were prepared by NaClO<sub>2</sub>-oxidation of the corresponding aldehydes reported in the following papers: a) J. Yoshida, M. Nakagawa, H. Seki, and T. Hino, *J. Chem. Soc., Perkin Trans. 1*, **1992**, 343. b) C. Hubschwerlen, *Synthesis*, **1986**, 962.
- a) F. N. Tebbe, G. W. Parshall, and G. S. Reddy, *J. Am. Chem. Soc.*, **100**, 3611 (1978). b) F. N. Tebbe, G. W. Parshall, and G. S. Reddy, *J. Am. Chem. Soc.*, **101**, 5074 (1979). c) S. H. Pine, R. Zahler, D. A. Evans, and R. H. Grubbs, *J. Am. Chem. Soc.*, **102**, 3270 (1980). d) S. H. Pine, G. Kim, and V. Lee, *Org. Synth.*, **69**, 72 (1990).
- Treatment of **8a** or **8b** with thexylborane followed by oxidation could not improve the ratio of **9** to **10**. In each case, the production of **5**, which would result from 1,2-elimination in the corresponding hydroboration product having a 2-alkoxyalkylborane system, was mainly observed.
- D. B. Dess and J. C. Martin, *J. Org. Chem.*, **48**, 4155 (1983).
- When Samuelsson's method (P. J. Garegg and B. Samuelsson, *Synthesis*, **1979**, 469) was applied to diol **20b**, the reaction could not finish and gave a mixture of the corresponding iodide and **21b**. Further treatment of the mixture with Zn was required for the complete conversion to **21b**.