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

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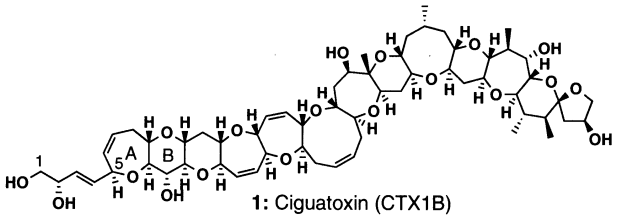
Asymmetric synthesis of the A-ring part of a marine toxin ciguatoxin (CTX1B) was achieved by the strategy based on ring closing metathesis (RCM), where introduction of the C5 asymmetric center was performed by diastereocontrolled hydroboration of a vinyl ether moiety.

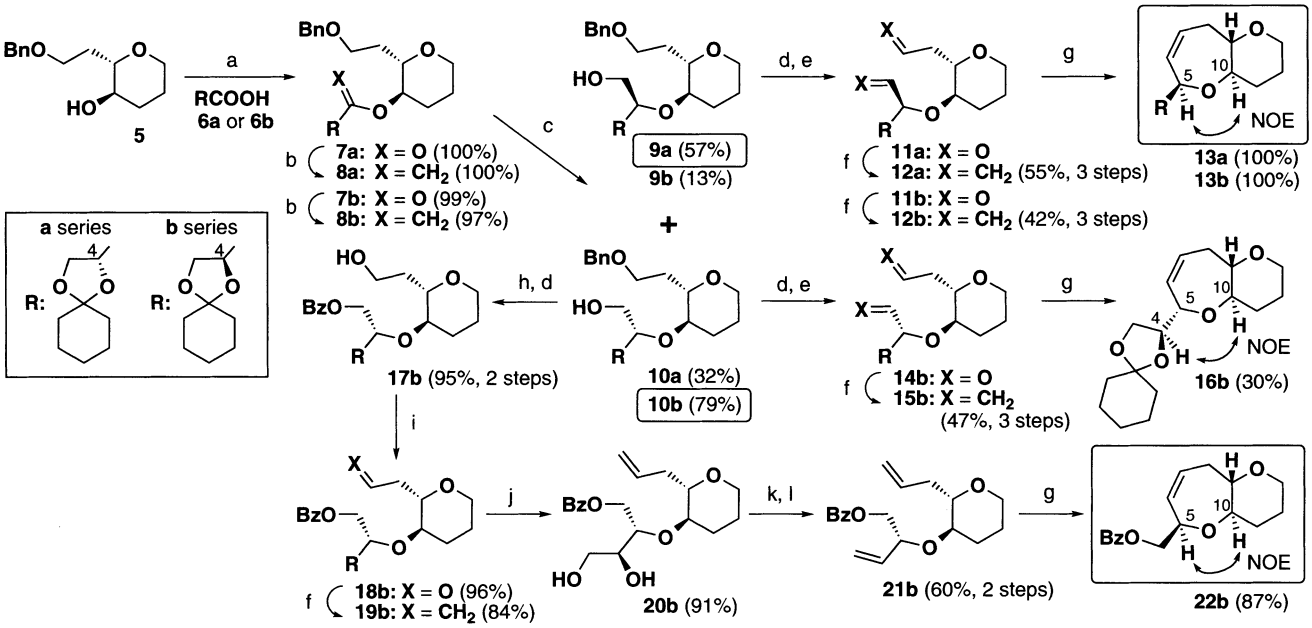
Ciguatoxin (CTX1B) **1**, which is one of the causative toxins of food poisoning, ciguatera, attracts much attention of synthetic chemists in its complex structure and strong bioactivity.[1-5] As a part of our synthetic study on **1**,[2] we have studied asymmetric synthesis of the A-ring part of **1**[3,4] based on ring closing metathesis (RCM).[6] During our study, Hirama group has reported the synthesis of the same part by C5[7]-stereoselective RCM.[5] 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[7] as a chiral auxiliary according to McGarvey's method.[8]



Scheme 1.

First, vinyl ether **8a** was prepared by esterification of chiral oxane **5**[9] with carboxylic acid **6a** derived from D-mannitol[10] followed by olefination of the resultant ester **7a** with Tebbe reagent[11] (Scheme 2). Hydroboration of **8a** with BH_3·THF followed by oxidation gave ethers **9a** and **10a** in 57% and 32% yields, respectively.[12] 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), CH_2Cl_2, 22-24 °C, 0.5-2 h; b) Cp_2TiCl_2 (1.5 eq), $AlMe_3$ (3 eq), toluene, 23 °C, 3 d, then **7**, THF-toluene (1:6-9), 0 → 23 °C, 20-30 min; c) [reaction of **8a**]: BH_3•THF (3.0 eq), THF, -30 °C, 14 h, then 5M NaOH (9.0 eq), 30% H_2O_2 (9.0 eq), 0 → 25 °C, 11 h; [reaction of **8b**]: BH_3•THF (1.5 eq), THF, 0 °C, 40 min, then 5 M NaOH (4.5 eq), 30% H_2O_2 (4.5 eq), 0 → 22 °C, 13 h; d) H_2, Pd/C, EtOH or MeOH, 22-25 °C, 4-19 h; e) Dess-Martin periodinane (5.1-5.5 eq), CH_2Cl_2, 22-24 °C, 1.5-3 h; f) $Ph_3P{=}CH_2$ (2.5-6.2 eq), THF, -78 → 0 °C, 0.7-13 h; g) $(Cy_3P)_2Cl_2Ru{=}CHPh$ (0.3-0.9 eq), CH_2Cl_2, reflux, 1-6 h; h) BzCl (5.0 eq), DMAP (0.5 eq), pyridine, 25 °C, 3.5 h; i) $(COCl)_2$ (4.5 eq), DMSO (7.2 eq), CH_2Cl_2, -78 °C, 25 min, then Et_3N (15 eq), -78 → 0 °C, 30 min; j) 3M HCl-THF (1:1), 27 °C, 30 h; k) PPh_3 (8 eq), 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. NH_4Cl (5:1), 26 °C, 6 h.

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

Next, we examined C4-epimeric **8b**, which was synthesized from **6b** originated from L-γ-gulonolactone[10] in the similar manner to **8a**. When **8b** was subjected to hydroboration with BH_3·THF followed by oxidation, **9b** and **10b** were produced in 13% and 79% yields, respectively.[12] 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,[8] 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 debenzylation 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.[14] 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 complemental routes based on RCM as well as diastereocontrolled hydroboration.

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